

FILE 'USPAT' ENTERED AT 16:21:01 ON 13 OCT 1997

* WELCOME TO THE *
* U.S. PATENT TEXT FILE *

=> s (igf## or (insulin?(3a)(growth factor?))
UNMATCHED LEFT PARENTHESIS '(IGF##'

=> s (igf## or (insulin?(3a)(growth factor?))
2164 IGF##
8553 INSULIN?
126611 GROWTH
392857 FACTOR?
7235 GROWTH FACTOR?
(GROWTH(W)FACTOR?)
1082 INSULIN?(3A)(GROWTH FACTOR?)
L1 2716 (IGF## OR (INSULIN?(3A)(GROWTH FACTOR?)))

=> s l1 and (nerv? or neur?)
22130 NERV?
23195 NEUR?
L2 706 L1 AND (NERV? OR NEUR?)

=> s (igf### or (insulin?(3a)(growth factor?))
2302 IGF###
8553 INSULIN?
126611 GROWTH
392857 FACTOR?
7235 GROWTH FACTOR?
(GROWTH(W)FACTOR?)
1082 INSULIN?(3A)(GROWTH FACTOR?)
L3 2854 (IGF### OR (INSULIN?(3A)(GROWTH
FACTOR?)))

=> s l3 and (nerv? or neur?)
22130 NERV?
23195 NEUR?
L4 706 L3 AND (NERV? OR NEUR?)

=> s l4 and (brain or (central(3a)(nerv? or neur?) or cns)
UNMATCHED LEFT PARENTHESIS 'AND (BRAIN'
YOU HAVE RECEIVED THIS ERROR MESSAGE 2
CONSECUTIVE TIMES
The number of right parentheses in a query must be equal to the
number of left parentheses.
IF YOU REQUIRE FURTHER HELP, PLEASE CONTACT
YOUR LOCAL HELP DESK

=> s l4 and (brain or (central(3a)(nerv? or neur?) or cns)
18911 BRAIN
549307 CENTRAL
22130 NERV?
23195 NEUR?
10045 CENTRAL(3A)(NERV? OR NEUR?)
3712 CNS
L5 361 L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS)

=> s l4 and (brain or (central(3a)(nerv? or neur?) or cns or spin?)
18911 BRAIN
549307 CENTRAL
22130 NERV?
23195 NEUR?
10045 CENTRAL(3A)(NERV? OR NEUR?)
3712 CNS
153712 SPIN?
L6 437 L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS OR SP
IN?
)

=> s l4 and (brain or (central(3a)(nerv? or neur?) or cns or spine or
spinal)

18911 BRAIN
549307 CENTRAL
22130 NERV?
23195 NEUR?
10045 CENTRAL(3A)(NERV? OR NEUR?)
3712 CNS
8242 SPINE
7284 SPINAL
L7 381 L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS OR SP
INE
OR SPINAL)

=> d 370-381

370. 4,863,899, Sep. 5, 1989, Biologically active polypeptides;
George
J. Todaro, 514/9, 10, 11, 12, 13, 14; 930/10, 120, DIG.821
:IMAGE
AVAILABLE:

371. 4,832,759, May 23, 1989, Microstructures; Adam S. G. Curtis,
et
al., 435/305.1 :IMAGE AVAILABLE:

372. 4,816,561, Mar. 28, 1989, Biologically active polypeptides;
George
J. Todaro, 530/324, 325, 326, 327; 930/120, DIG.811, DIG.821
:IMAGE
AVAILABLE:

373. 4,801,575, Jan. 31, 1989, Chimeric peptides for
neuropeptide
delivery through the blood-**brain** barrier; William M. Pardridge,
514/4; 424/85.7; 514/2, 3; 530/302, 303, 311, 351; 930/21, 24, 80,
150,
160, 260, DIG.565, DIG.570, DIG.620, DIG.700, DIG.720
:IMAGE AVAILABLE:

374. 4,779,806, Oct. 25, 1988, Ultrasonically modulated polymeric
devices for delivering compositions; Robert S. Langer, et al., 241/1;
222/1; 241/2, 30 :IMAGE AVAILABLE:

375. 4,727,041, Feb. 23, 1988, Method of diagnosing Alzheimer's
disease;
Chaovanee Aroonsakul, 436/8, 87, 500, 811 :IMAGE
AVAILABLE:

376. 4,716,887, Jan. 5, 1988, Apparatus and method for adjusting
heart/pacer rate relative to cardiac pCO.sub.2 to obtain a required
cardiac output; Gerrit Koning, et al., 607/24; 128/635; 607/16, 22
:IMAGE
AVAILABLE:

377. 4,703,008, Oct. 27, 1987, DNA sequences encoding
erythropoietin;
Fu-Kuen Lin, 435/360, 6, 172.3, 252.3, 252.33, 320.1, 365.1;
536/23.51,
23.72, 24.1, 24.3, 24.31, 25.32; 930/90; 935/9, 10, 13, 79, 80
:IMAGE
AVAILABLE:

378. 4,666,704, May 19, 1987, Controlled release delivery system
for
macromolecules; Mohamad D. Shalati, et al., 424/424, 491, DIG.7;
514/2,
964, 965 :IMAGE AVAILABLE:

379. 4,661,453, Apr. 28, 1987, Production of tissue plasminogen activator factor; Morris Pollard, 435/212, 215, 219 :IMAGE AVAILABLE:

380. 4,657,543, Apr. 14, 1987, Ultrasonically modulated polymeric devices for delivering compositions; Robert S. Langer, et al., 424/486; 601/2; 604/22, 49, 290 :IMAGE AVAILABLE:

381. 4,440,860, Apr. 3, 1984, Stimulating cell growth; Michael Klagsbrun, 435/384; 424/85.1; 435/289.1, 387, 389, 391, 402, 406, 408 :IMAGE AVAILABLE:

=> d 373 date

L7: 373 of 381

TITLE: Chimeric peptides for **neuropeptide** delivery through

the blood-**brain** barrier

US PAT NO: 4,801,575 DATE ISSUED: Jan. 31, 1989 :IMAGE AVAILABLE:

APPL-NO: 06/891,867 DATE FILED: Jul. 30, 1986

=> d 373 ab

US PAT NO: 4,801,575 :IMAGE AVAILABLE: L7: 373 of 381

ABSTRACT:

Chimeric peptides adapted for delivering **neuropharmaceutical** agents, such as **neuropeptides** into the **brain** by receptor-mediated transcytosis through the blood-**brain** barrier. The chimeric peptides include a peptide which by itself is capable of crossing the blood-**brain** barrier by transcytosis at a relatively high rate. The transportable peptide is conjugated to a hydrophilic **neuropeptide** which by itself is transportable only at a very low rate into the **brain** across the blood-**brain** barrier. The resulting chimeric peptide is transported into the **brain** at a much higher rate than the **neuropeptide** alone to thereby provide an effective means for introducing hydrophilic **neuropeptides** into the **brain** through the blood-**brain** barrier.

=> d 373 kwic

US PAT NO: 4,801,575 :IMAGE AVAILABLE: L7: 373 of 381

TITLE: Chimeric peptides for **neuropeptide** delivery through the blood-**brain** barrier

ABSTRACT:

Chimeric peptides adapted for delivering **neuropharmaceutical** agents, such as **neuropeptides** into the **brain** by receptor-mediated transcytosis through the blood-**brain** barrier. The chimeric peptides include a peptide which by itself is capable of crossing the blood-**brain** barrier by transcytosis at a relatively high rate. The transportable peptide is conjugated to a hydrophilic **neuropeptide** which by itself is transportable only at a very low rate into the **brain** across the blood-**brain** barrier. The resulting chimeric peptide is transported into the **brain** at a much higher rate than the **neuropeptide** alone to thereby provide an effective means for introducing hydrophilic **neuropeptides** into the **brain** through the

blood-**brain** barrier.

SUMMARY:

BSUM(2)

The present invention relates generally to the introduction of **neuropharmaceutical** agents into the **brain** by transcytosis across the blood-**brain** barrier. More particularly, the present invention relates to chimeric peptides which are capable of transporting **neuropharmaceutical** agents into the **brain** by receptor-mediated transcytosis across the blood-**brain** barrier.

SUMMARY:

BSUM(3)

The vertebrate **brain** has a unique capillary system which is unlike that in any other organ in the body. The unique capillary system has morphologic characteristics which make up the blood-**brain** barrier (BBB). The blood-**brain** barrier acts as a systemwide cellular membrane which separates the **brain** interstitial space from the blood.

SUMMARY:

BSUM(4)

The unique morphologic characteristics of the **brain** capillaries which make up the BBB are: (a) epithelial-like high resistance tight junctions which literally cement all endothelia of **brain** capillaries together, and (b) scanty pinocytosis or transendothelial channels, which are abundant in endothelia of peripheral organs. Due to the unique characteristics of the blood-**brain** barrier, hydrophilic drugs and peptides that readily gain access to other tissues in the body are barred from entry into the **brain** or their rates of entry are very low.

SUMMARY:

BSUM(5)

Various strategies have been developed for introducing those drugs into the **brain** which otherwise would not cross the blood-**brain** barrier. The most widely used strategies involve invasive procedures where the drug is delivered directly into the **brain**. The most common procedure is the implantation of a catheter into the ventricular system to bypass the blood-**brain** barrier and deliver the drug directly to the **brain**. These procedures have been used in the treatment of **brain** diseases which have a predilection for the meninges, e.g., leukemic involvement of the **brain**.

SUMMARY:

BSUM(6)

Although invasive procedures for the direct delivery of drugs to the **brain** ventricles have experienced some success, they have not been entirely successful because they only distribute the drug to superficial areas of the **brain** tissues, and not to the structures deep within the **brain**. Further, the invasive procedures are potentially harmful to

the patient.

SUMMARY:

BSUM(7)

Other approaches to circumventing the blood-**brain** barrier utilize pharmacologic-based procedures involving drug latentiation or the conversion of hydrophilic drugs into lipid-soluble drugs. The majority of the . . . carboxyl and primary amine groups on the drug to make it more lipid-soluble and therefore more easily transported across the blood-**brain** barrier. Although the pharmacologic approaches have been used with some success, they may not be entirely satisfactory for delivery of. . .

SUMMARY:

BSUM(8)

Another approach to circumventing the blood-**brain** barrier involves the intra-arterial infusion of hypertonic substances which transiently open the blood-**brain** barrier to allow passage of hydrophilic drugs. However, hypertonic substances are potentially toxic and may damage the blood-**brain** barrier.

SUMMARY:

BSUM(9)

There presently is a need to provide improved substances and methods for delivering hydrophilic drugs and peptides across the blood-**brain** barrier and into the **brain**. It is desirable that such improved substances and methods provide for uniform introduction of the hydrophilic peptide or drug throughout the **brain** and present as little risk to the patient as possible.

SUMMARY:

BSUM(11)

In accordance with the present invention, new procedures and substances are disclosed which provide uniform distribution of **neuropeptides** and other drugs throughout the **brain** while reducing the problems inherent in prior invasive and pharmacologic drug introduction procedures.

SUMMARY:

BSUM(12)

The present invention is based on the surprising discovery that hydrophilic peptides may be physiologically transported across the blood-**brain** barrier by coupling or conjugating the drug to a transportable peptide which is capable of crossing the blood-**brain** barrier by receptor-mediated transcytosis. This discovery is particularly surprising in view of the traditional notion that the blood-**brain** barrier is a passive barrier which is impenetrable by hydrophilic drugs or peptides.

SUMMARY:

BSUM(13)

The invention involves novel chimeric peptides which are adapted to deliver a **neuropharmaceutical** agent into the **brain** by transcytosis across the blood-**brain** barrier. The chimeric peptides include a transportable peptide that is capable of crossing the blood-**brain** barrier at relatively high rate by receptor-mediated transcytosis. The transportable peptide is conjugated with a **neuropharmaceutical** agent to form the chimeric peptide. The **neuropharmaceutical** agent is generally a hydrophilic peptide that does not by itself significantly cross the BBB. The conjugation of transportable peptides with **neuropharmaceutical** agents was surprisingly found to produce chimeric peptides which were capable of being transported across the blood-**brain** barrier.

SUMMARY:

BSUM(14)

As a feature of the present invention, the chimeric peptides are believed to be transported across the blood-**brain** barrier by the physiologic process of transcytosis via receptors in the blood-**brain** barrier. This insures that the chimeric peptide is distributed uniformly to all parts of the **brain**. In addition, the introduction of the chimeric peptide into the **brain** by a physiologic pathway reduces the harmful side effects and risks inherent in the traditional invasive and pharmacological approaches.

DETDESC:

DETD(2)

The chimeric peptides in accordance with the present invention are useful in delivering a wide variety of **neuropharmaceutical** agents to the **brain**. The invention is particularly well suited for delivering **neuropharmaceutical** agents which are hydrophilic peptides. These hydrophilic peptides are generally not transported across the blood-**brain** barrier to any significant degree.

DETDESC:

DETD(3)

Exemplary hydrophilic peptide **neuropharmaceutical** agents are: thyrotropin releasing hormone (TRH)—used to treat **spinal** cord injury and Lou Gehrig's disease; vasopressin—used to treat amnesia; alpha interferon—used to treat multiple sclerosis; somatostatin—used to treat Alzheimer's. . . L-methionyl (sulfone)-L-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-L-phenylalanine (an analogue of adrenocorticotrophic hormone (ACTH)-4-9)—used to treat epilepsy; and muramyl dipeptide—used to treat insomnia. All of these **neuropharmaceutical** peptides are available commercially or they may be isolated from natural sources by well-known techniques.

DETDESC:

DETD(4)

The following description will be limited to chimeric peptides in which the **neuropharmaceutical** agents are hydrophilic peptides (**neuropeptides**) with it being understood that the invention has application to any **neuropharmaceutical** agent which by itself is transported at a low or non-existent rate across the blood-**brain** barrier. The invention also has application where it is desired to increase the rate at which the **neuropharmaceutical** agent is transported across the blood-**brain** barrier.

DETD(5):

DETD(5)

The chimeric peptide includes the hydrophilic peptide drug conjugated to a transportable peptide which is capable of crossing the blood-**brain** barrier by transcytosis at a much higher rate than the hydrophilic **neuropeptides**. Suitable transportable peptides include: **insulin**, **transferrin**, **insulin-like growth factor I** (**IGF-I**), **insulin-like growth factor II** (**IGF-II**), basic albumin and prolactin.

DETD(7):

DETD(7)

Insulin, **IGF-I** and **IGF-II** are also commonly available. Insulin is available on a wide scale commercially and may also be recovered from natural sources by well-known techniques. **IGF-I** and **IGF-II** are available from commercial outlets such as Amgen or Peninsula Labs or they may be isolated from natural sources according to . . .

DETD(8):

DETD(8)

Basic . . . (pI) of 8.5 as compared to a pI of 3.9 for natural albumin. Cationized albumin, unlike natural albumin, enters the **brain** rapidly across the blood-**brain** barrier. Cationized albumin (pI=8.5) is prepared preferably by covalent coupling of hexamethylene-diamine (HMD) to bovine serum albumin (pI=3.5) according to . . .

DETD(10):

DETD(10)

The chimeric peptides are made by conjugating a transportable peptide with the **neuropharmaceutical** peptide.

DETD(11):

DETD(11)

The . . . transportable peptide) together without denaturing them. Preferably, the linkage can be easily broken once the chimeric peptide has entered the **brain**. Suitable examples of conjugation reagents include: glutaraldehyde and cystamine and EDAC. Conjugation of peptides

using glutaraldehyde is described in Poznansky. . .

DETD(12):

DETD(12)

Examples . . . is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and B is insulin, **IGF-I**, **IGF-II**, transferrin, cationized (basic) albumin or prolactin.

DETD(18):

DETD(18)

The . . . The concentration of a chimeric peptide in the carrier will vary depending upon the specific transportable peptide and the specific **neuropharmaceutical** peptide. Preferably, levels of the chimeric peptide in the carrier should be between about 0.001 weight percent to 0.01 weight. . . chimeric peptides present in the injection or intranasal solution should correspond to the accepted and established dosages for the particular **neuropharmaceutical** peptide as well as the transportable peptide.

DETD(22):

DETD(22)

Somatostatin, a peptide deficient in the **brain** of Alzheimer's disease, is a peptide which is not transported through the blood-**brain** barrier. Conversely, insulin is a peptide that is transported through the blood-**brain** barrier. The transportability of insulin through the blood-**brain** barrier is set forth in my article entitled "Receptor-Mediated Peptide Transport Through The Blood-**Brain** Barrier" (Endocrine Reviews, Vol. 7, No. 3, August 1986), the contents of which is hereby incorporated by reference.

DETD(29):

DETD(29)

Brain Microvessels and .sup.3 H-Somatostatin-.sup.125 I-Insulin Chimera

DETD(30):

DETD(30)

Somatostatin . . . using chloramine T and .sup.125 I-iodine. The two compounds were coupled together using SPDP as described in Example 1. Bovine **brain** microvessels were isolated as described in Pardridge, et al., "Rapid Sequestration And Degradation Of Somatostatin Analogues By Isolated **Brain** Microvessels", (Journal of **Neurochemistry**, Vol. 44, No. 4, 1985, pp. 1178-1184).

DETD(31):

DETD(31)

.sup.3 . . . somatostatin. The uptake of the free somatostatin likely represents nonspecific binding as described in the article mentioned above (Journal of **Neurochemistry**, Vol. 44, No. 4, 1985).

DETDESC:

DETD(32)

This . . . of somatostatin-insulin chimera via the insulin receptor. Previous studies have shown that the receptor-mediated endocytosis of peptides in the isolated **brain** microvessels is a reliable index of the in vivo blood-**brain** barrier receptor transport activity of peptides in vivo (see my previously-mentioned article in Endocrine Reviews, Vol. 7, No. 3, August. . .

DETDESC:

DETD(40)

A chimeric peptide is prepared according to the same procedure as in Example 1 except that **IGF**-II is coupled to beta-endorphin. The resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight. . .

CLAIMS:

CLMS(1)

What is claimed is:

1. A chimeric peptide adapted for delivering a **neuropharmaceutical** agent into the **brain** by transcytosis through the blood-**brain** barrier, said chimeric peptide comprising: a transportable peptide capable of crossing the blood-**brain** barrier by transcytosis, said peptide being selected from the group consisting of insulin, transferrin, **IGF**-I, **IGF**-II, basic albumin and prolactin; and a **neuropharmaceutical** agent selected from the group consisting of somatostatin, thyrotropin releasing hormone, vasopressin, alpha interferon, endorphin, muramyl dipeptide and L-methionyl(sulfone)-L-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-L-phenylalanine, wherein said **neuropharmaceutical** agent is conjugated with said transportable peptide.

CLAIMS:

CLMS(2)

2. A chimeric peptide according to claim 1 wherein said transportable peptide and **neuropharmaceutical** agent are conjugated via a conjugation agent.

CLAIMS:

CLMS(3)

3. A chimeric peptide according to claim 2 wherein said conjugation agent is capable of conjugating the transportable peptide to said **neuropharmaceutical** agent by peptide thiolation or lysine coupling via glutaraldehyde.

CLAIMS:

CLMS(5)

5. A chimeric peptide according to claim 4 wherein said **neuropharmaceutical** agent is somatostatin.

CLAIMS:

CLMS(6)

6. A chimeric peptide according to claim 1 having the formula ##STR3## wherein A is said **neuropharmaceutical** agent and B is said transportable peptide.

CLAIMS:

CLMS(10)

10. A method for delivering a **neuropharmaceutical** agent into the **brain** of an animal by transcytosis through the blood-**brain** barrier comprising the step of introducing a chimeric peptide into the bloodstream of said animal in a sufficient amount to provide transport of said chimeric peptide across said blood-**brain** barrier, wherein said chimeric peptide comprises a transportable peptide capable of crossing the blood-**brain** barrier conjugated with a **neuropharmaceutical** agent.

CLAIMS:

CLMS(12)

12. In a method for introducing a **neuropharmaceutical** agent into the **brain** across the blood-**brain** barrier, wherein the improvement comprises increasing the rate at which said **neuropharmaceutical** agent crosses the blood-**brain** barrier by conjugating said **neuropharmaceutical** agent with a transportable peptide capable of crossing the blood-**brain** carrier by transcytosis.

CLAIMS:

CLMS(13)

13. A method according to claim 10 wherein said transportable peptide is selected from the group consisting of insulin, transferrin, **IGF**-I, **IGF**-II, basic albumin and prolactin.

CLAIMS:

CLMS(14)

14. A method according to claim 10 wherein said **neuropharmaceutical** agent is a hydrophilic peptide.

CLAIMS:

CLMS(15)

15. A method according to claim 14 wherein said
neuropharmaceutical
agent is selected from the group consisting of somatostatin,
thyrotropin
releasing hormone, vasopressin, alpha interferon, endorphin,
muramyl
dipeptide and L-methionyl(sulfone)-L-glutamyl-L-histidyl-L-
phenylalanyl-D-
lysyl-L-phenylalanine.

CLAIMS:

CLMS(16)

16. A method according to claim 10 wherein said transportable
peptide
and **neuropharmaceutical** agent are conjugated via a conjugation
agent.

CLAIMS:

CLMS(17)

17. A method according to claim 16 wherein said conjugation agent
is
capable of conjugating the transportable peptide to said
neuropharmaceutical agent by peptide thiolation or lysine
coupling
via glutaraldehyde.

CLAIMS:

CLMS(19)

19. A method according to claim 18 wherein said
neuropharmaceutical
agent is somatostatin.

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L1 2716 S (IGF## OR (INSULIN?(3A)(GROWTH
FACTOR?)))
L2 706 S L1 AND (NERV? OR NEUR?)
L3 2854 S (IGF### OR (INSULIN?(3A)(GROWTH
FACTOR?)))
L4 706 S L3 AND (NERV? OR NEUR?)
L5 361 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS)
L6 437 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS OR
SP
L7 381 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS OR
SP

=> s 17 and (parenteral(5a)administrat?)

32708 PARENTERAL
81011 ADMINISTRAT?

24215 PARENTERAL(5A)ADMINISTRAT?

L8 69 L7 AND (PARENTERAL(5A)ADMINISTRAT?)

=> d 50-69

50. 5,364,851, Nov. 15, 1994, Conformationally restricted
biologically
active peptides, methods for their production and uses thereof; Alvin
D.
Joran, 530/345; 204/157.82; 205/435; 530/303, 311, 312, 315
:IMAGE
AVAILABLE:

51. 5,331,094, Jul. 19, 1994, Purified active somatostatin receptor;
Cecil M. Eppler, et al., 530/395, 350 :IMAGE AVAILABLE:

52. 5,316,754, May 31, 1994, In vitro assay of mesangial cell-
derived
receptors for advanced glycosylation endproducts; Helen Vlassara, et
al.,
435/6, 3, 4, 7.1, 7.9, 30; 530/350, 380, 395, 397, 398, 399 :IMAGE
AVAILABLE:

53. 5,310,881, May 10, 1994, Glycosaminoglycan-modified
protein;
Katsukiyo Sakurai, et al., 530/395 :IMAGE AVAILABLE:

54. 5,273,961, Dec. 28, 1993, Method of prophylaxis of acute renal
failure; Ross G. Clark, 514/8, 12, 21 :IMAGE AVAILABLE:

55. 5,243,094, Sep. 7, 1993, Derivatives of long chain fatty
alcohols,
their uses, particularly as cytotropic and cytoprotective molecules,
and
pharmaceutical compositions containing them; Jacques Borg,
568/822, 667,
668, 824 :IMAGE AVAILABLE:

56. 5,240,912, Aug. 31, 1993, Transforming growth factor (TGF)
peptides;
George J. Todaro, 514/12, 13, 14, 15, 16; 530/324, 325, 326, 327,
328
:IMAGE AVAILABLE:

57. 5,234,906, Aug. 10, 1993, Hyperglycemic compositions;
Andrew Young,
et al., 514/12, 21 :IMAGE AVAILABLE:

58. 5,229,501, Jul. 20, 1993, Expression and use of human
fibroblast
growth factor receptor; Michael C. Keifer, et al., 530/399 :IMAGE
AVAILABLE:

59. 5,202,424, Apr. 13, 1993, Mesangial cell-derived receptors for
advanced glycosylation endproducts and uses thereof; Helen
Vlassara, et
al., 530/395; 435/7.1, 7.9; 530/380, 397, 399 :IMAGE
AVAILABLE:

60. 5,202,119, Apr. 13, 1993, Method of stimulating immune
response;
Ross G. Clark, et al., 424/204.1, 234.1, 277.1, 278.1; 514/2, 3
:IMAGE
AVAILABLE:

61. 5,166,191, Nov. 24, 1992, Use of relaxin in cardiovascular
therapy;
Michael Cronin, et al., 514/12; 530/324 :IMAGE AVAILABLE:

62. 5,128,320, Jul. 7, 1992, Method of restoring normal growth,
weight
gain or lean body mass in patients with glucocorticoid excess by
administering **IGF**-I; Theodore J. Hahn, et al., 514/12, 21
:IMAGE
AVAILABLE:

63. 5,108,921, Apr. 28, 1992, Method for enhanced transmembrane
transport of exogenous molecules; Philip S. Low, et al., 435/375,
243;
514/2, 44; 935/52 :IMAGE AVAILABLE:

64. 5,093,317, Mar. 3, 1992, Treating disorders by application of

****insulin**-like ****growth**** ****factor******; Michael E. Lewis, et al.,
514/12;
424/556, 570; 514/3, 4, 21, 885, 903 :IMAGE AVAILABLE:

65. 5,089,475, Feb. 18, 1992, Treatment of ventilator dependency
with
growth hormone; Douglas W. Wilmore, 514/12, 885, 924, 926
:IMAGE
AVAILABLE:

66. 5,057,494, Oct. 15, 1991, Method for preventing tissue damage
after
an ischemic episode; Warren D. Sheffield, 514/12, 21 :IMAGE
AVAILABLE:

67. 4,863,902, Sep. 5, 1989, Treatment of cancer; Harunobu
Amagase, et
al., 514/12, 2, 21 :IMAGE AVAILABLE:

68. 4,863,899, Sep. 5, 1989, Biologically active polypeptides;
George J.
Todaro, 514/9, 10, 11, 12, 13, 14; 930/10, 120, DIG.821 :IMAGE
AVAILABLE:

69. 4,816,561, Mar. 28, 1989, Biologically active polypeptides;
George
J. Todaro, 530/324, 325, 326, 327; 930/120, DIG.811, DIG.821
:IMAGE
AVAILABLE:

=> s 4801575/pn
L9 1 4801575/PN

=> s l9 and administer?
80499 ADMINISTER?
L10 1 L9 AND ADMINISTER?

=> d kwic
US PAT NO: ****4,801,575**** :IMAGE AVAILABLE: L10: 1
of 1

SUMMARY:

BSUM(15)

The present invention also includes methods for ****administering****
the
chimeric peptides subcutaneously or intranasally and the chimeric
peptide
containing compositions utilized in such methods of treatment.

DETDESC:

DETD(18)

The . . . peptides are combined with a compatible pharmaceutical
carrier and injected parenterally or if desired combined with a
suitable
carrier and ****administered**** intranasally in accordance with the
well-known conventional procedures used for intranasal
administration of
insulin. Suitable carrier solutions include those commonly. . .

DETDESC:

DETD(34)

A . . . resulting chimeric peptide is combined with sterile saline to
provide a solution containing 0.01 weight percent chimeric peptide
which
is ****administered**** to the patient parenterally or intranasally.

DETDESC:

DETD(36)

A . . . resulting chimeric peptide is combined with sterile saline to
provide a solution containing 0.01 weight percent chimeric peptide
which
is ****administered**** to the patient parenterally.

DETDESC:

DETD(38)

A . . . resulting chimeric peptide is combined with sterile saline to
provide a solution containing 0.01 weight percent chimeric peptide
which
is ****administered**** to the patient or subject parenterally or
intranasally.

DETDESC:

DETD(40)

A . . . resulting chimeric peptide is combined with sterile saline to
provide a solution containing 0.01 weight percent chimeric peptide
which
is ****administered**** to the patient or subject parenterally or
intranasally.

DETDESC:

DETD(42)

A . . . resulting chimeric peptide is combined with sterile saline to
provide a solution containing 0.01 weight percent chimeric peptide
which
is ****administered**** to the patient or subject parenterally or
intranasally.

DETDESC:

DETD(44)

A . . . resulting chimeric peptide is combined with sterile saline to
provide a solution containing 0.01 weight percent chimeric peptide
which
is ****administered**** to the patient or subject parenterally or
intranasally.

=> d his

(FILE 'USPAT' ENTERED AT 16:21:01 ON 13 OCT 1997)

L1 2716 S (IGF## OR (INSULIN?(3A)(GROWTH
FACTOR?)))

L2 706 S L1 AND (NERV? OR NEUR?)

L3 2854 S (IGF### OR (INSULIN?(3A)(GROWTH
FACTOR?)))

L4 706 S L3 AND (NERV? OR NEUR?)

L5 361 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS)

L6 437 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS OR

SP

L7 381 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR
NEUR?)) OR CNS OR

SP

L8 69 S L7 AND (PARENTERAL(5A)ADMINISTRAT?)

L9 1 S 4801575/PN

L10 1 S L9 AND ADMINISTER?

=> s 17 and (parenteral?(10A)administ?)
 41568 PARENTERAL?
 98704 ADMINIST?
 36037 PARENTERAL?(10A)ADMINIST?
 L11 108 L7 AND (PARENTERAL?(10A)ADMINIST?)

=> d 90-108

90. 5,229,501, Jul. 20, 1993, Expression and use of human fibroblast growth factor receptor; Michael C. Keifer, et al., 530/399 :IMAGE AVAILABLE:

91. 5,215,969, Jun. 1, 1993, Dopaminergic ****neurotrophic**** factor for treatment of Parkinson's disease; Joe E. Springer, et al., 514/21, 2 :IMAGE AVAILABLE:

92. 5,203,768, Apr. 20, 1993, Transdermal delivery device; Ronald P. Haak, et al., 604/20, 49; 607/152 :IMAGE AVAILABLE:

93. 5,202,424, Apr. 13, 1993, Mesangial cell-derived receptors for advanced glycosylation endproducts and uses thereof; Helen Vlassara, et al., 530/395; 435/7.1, 7.9; 530/380, 397, 399 :IMAGE AVAILABLE:

94. 5,202,119, Apr. 13, 1993, Method of stimulating immune response; Ross G. Clark, et al., 424/204.1, 234.1, 277.1, 278.1; 514/2, 3 :IMAGE AVAILABLE:

95. 5,183,809, Feb. 2, 1993, Cyclodextrin polymers and cyclodextrins immobilized on a solid surface; Paul B. Weisz, et al., 514/58; 428/423.1, 426, 447, 532; 530/810, 812, 813; 536/103 :IMAGE AVAILABLE:

96. 5,166,191, Nov. 24, 1992, Use of relaxin in cardiovascular therapy; Michael Cronin, et al., 514/12; 530/324 :IMAGE AVAILABLE:

97. 5,128,320, Jul. 7, 1992, Method of restoring normal growth, weight gain or lean body mass in patients with glucocorticoid excess by administering ****IGF****-I; Theodore J. Hahn, et al., 514/12, 21 :IMAGE AVAILABLE:

98. 5,115,096, May 19, 1992, Amphiregulin: a bifunctional growth modulating glycoprotein; Mohammed Shoyab, et al., 530/322, 324 :IMAGE AVAILABLE:

99. 5,108,921, Apr. 28, 1992, Method for enhanced transmembrane transport of exogenous molecules; Philip S. Low, et al., 435/375, 243; 514/2, 44; 935/52 :IMAGE AVAILABLE:

100. 5,093,317, Mar. 3, 1992, Treating disorders by application of ****insulin****-like ****growth**** ****factor****; Michael E. Lewis, et al., 514/12; 424/556, 570; 514/3, 4, 21, 885, 903 :IMAGE AVAILABLE:

101. 5,089,475, Feb. 18, 1992, Treatment of ventilator dependency with growth hormone; Douglas W. Wilmore, 514/12, 885, 924, 926 :IMAGE

AVAILABLE:

102. 5,057,494, Oct. 15, 1991, Method for preventing tissue damage after an ischemic episode; Warren D. Sheffield, 514/12, 21 :IMAGE AVAILABLE:

103. 4,902,505, Feb. 20, 1990, Chimeric peptides for ****neuropeptide**** delivery through the blood-****brain**** barrier; William M. Pardridge, et al., 424/85.7; 514/2, 3, 4; 530/302, 303, 311, 350, 351 :IMAGE AVAILABLE:

104. 4,863,902, Sep. 5, 1989, Treatment of cancer; Harunobu Amagase, et al., 514/12, 2, 21 :IMAGE AVAILABLE:

105. 4,863,899, Sep. 5, 1989, Biologically active polypeptides; George J. Todaro, 514/9, 10, 11, 12, 13, 14; 930/10, 120, DIG.821 :IMAGE AVAILABLE:

106. 4,816,561, Mar. 28, 1989, Biologically active polypeptides; George J. Todaro, 530/324, 325, 326, 327; 930/120, DIG.811, DIG.821 :IMAGE AVAILABLE:

107. 4,801,575, Jan. 31, 1989, Chimeric peptides for ****neuropeptide**** delivery through the blood-****brain**** barrier; William M. Pardridge, 514/4; 424/85.7; 514/2, 3; 530/302, 303, 311, 351; 930/21, 24, 80, 150, 160, 260, DIG.565, DIG.570, DIG.620, DIG.700, DIG.720 :IMAGE AVAILABLE:

108. 4,703,008, Oct. 27, 1987, DNA sequences encoding erythropoietin; Fu-Kuen Lin, 435/360, 6, 172.3, 252.3, 252.33, 320.1, 365.1; 536/23.51, 23.72, 24.1, 24.3, 24.31, 25.32; 930/90; 935/9, 10, 13, 79, 80 :IMAGE AVAILABLE:

=> d 108 kwic

US PAT NO: 4,703,008 :IMAGE AVAILABLE: L11:
 108 of 108

SUMMARY:

BSUM(22)

It . . . menstrual disorders); Haga, et al., Acta.Pediatr.Scand., 72, 827-831 (1983) (early anemia of prematurity); Claus-Walker, et al., Arch.Phys.Med.Rehabil., 65, 370-374 (1984), (****spinal**** cord injury); Dunn, et al., Eur.JAppl.Physiol., 52, 178-182 (1984) (space flight); Miller, et al., Brit.J.Haematol., 52, 545-590 (1982), (acute blood. . .

DETDESC:

DETD(33)

Transformed . . . plates containing 50 micrograms/ml Ampicillin. GeneScreen filters (New England Nuclear Catalog No. NEF-972) were pre-wet on a BHI-CAM plate (Bacto ****brain**** heart infusion 37 g/L, Casamino acids

2 g/L and agar 15 g/L, containing 500 micrograms/ml Chloramphenicol) and were used to. . .

DETDESC:

DETD(98)

A . . . expression product which, in turn, was slightly larger than the pooled source human urinary extract. All products were somewhat heterogeneous. ****Neuraminidase**** enzyme treatment to remove sialic acid resulted in COS-1 and CHO recombinant products of approximately equal molecular weight which were. . .

DETDESC:

DETD(129)

A preferred method for ****administration**** of polypeptide products of the invention is by ****parenteral**** (e.g., IV, IM, SC, or IP) routes and the compositions administered would ordinarily include therapeutically effective amounts of product in. . .

DETDESC:

DETD(130)

Adjuvant . . . use in compositions of the invention include compounds independently noted for erythropoietic stimulatory effects, such as testosterone, progenitor cell stimulators, ****insulin****-like ****growth**** ****factor****, prostaglandins, serotonin, cyclic AMP, prolactin and triiodothyronine, as well as agents generally employed in treatment of aplastic anemia, such as. . .

=> d 106 kwic

US PAT NO: 4,816,561 :IMAGE AVAILABLE: L11:
106 of 108

SUMMARY:

BSUM(4)

A . . . tissue fluids and their relationship in the control of normal cellular growth or mitosis has been established. These mitogenic polypeptide ****growth**** ****factors**** include ****insulin****, ****insulin****-like ****growth**** ****factors****, platelet-derived growth factor, ****nerve**** growth factor, fibroblast growth factor and epidermal growth factor (EGF). At least some of these known growth factors have an. . . than do normal cells. In particular, it has been shown, in experiments in cell culture, that the addition of exogenous ****growth**** ****factors**** such as ****insulin**** and EGF can cause normal cells to mimic certain changes in cellular properties that are analogous to transformation; however, they. . .

SUMMARY:

BSUM(11)

Marquardt . . . stimulate phosphorylation of a synthetic

tyrosine-containing peptide. The only other molecules so far described that have this activity are EGF, ****insulin**** and platelet derived ****growth**** ****factor****, all of which are believed to have important physiologic functions in man and animal. Other references of interest are cited. . .

SUMMARY:

BSUM(83)

Methods . . . an active ingredient will normally be formulated with an appropriate solid or liquid carrier depending upon the particular mode of ****administration**** being used. For instance, ****parenteral**** formulations are usually injectable fluids that use pharmaceutically and physiologically acceptable fluids such as physiological saline, balanced salt solutions, or. . .

DETDESC:

DETD(6)

hTGFs . . . human metastatic melanoma line A2058 (Todaro et al. (1980) Proc. Natl. Acad. Sci. USA 77, pp. 5258-5262) derived from a ****brain**** metastasis in a 43-year-old man. Cells were grown to 90% confluency in roller bottles containing Dulbecco's modified Eagle's medium (Grand. . .

DETDESC:

DETD(84)

Three . . . in firm contact with the bare skin for exactly 10 seconds. Five wounds were placed on each side of the ****spine**** and were separated from each other by approximately 1 inch. The top of each resulting blister was totally removed and. . .

=> d 106 ab

US PAT NO: 4,816,561 :IMAGE AVAILABLE: L11:
106 of 108

ABSTRACT:

Novel biologically active polypeptides, including a new class of transforming growth factor (TGF) polypeptides, which exhibit cell growth promoting properties are disclosed, as well as a process for isolating the TGF polypeptides from both human and murine cell lines in homogeneous form. Also disclosed are antigenic oligopeptides derived from the TGF polypeptides and antibodies raised therefrom which have application in the detection and treatment of malignancies and oligopeptides which have the ability to bind with cellular growth factor receptors and thus to interfere with transformation of certain cell lines into a cancerous state. Compositions and methods based on the disclosed peptides for detection and treatment of cancer and other proliferative diseases and for cell or tissue growth associated treatment, e.g., wound healing, ulcer therapy and bone loss are also described.

=> d his

(FILE 'USPAT' ENTERED AT 16:21:01 ON 13 OCT 1997)

L1 2716 S (IGF## OR (INSULIN?(3A)(GROWTH FACTOR?)))
 L2 706 S L1 AND (NERV? OR NEUR?)
 L3 2854 S (IGF### OR (INSULIN?(3A)(GROWTH FACTOR?)))
 L4 706 S L3 AND (NERV? OR NEUR?)
 L5 361 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR NEUR?)) OR CNS)
 L6 437 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR NEUR?)) OR CNS OR
 SP
 L7 381 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR NEUR?)) OR CNS OR
 SP
 L8 69 S L7 AND (PARENTAL(5A)ADMINISTRAT?)
 L9 1 S 4801575/PN
 L10 1 S L9 AND ADMINISTER?
 L11 108 S L7 AND (PARENTAL?(10A)ADMINIST?)

=> s l11 and (alzheimer? or parkinson? or AIDS or hiv)
 2643 ALZHEIMER?
 3192 PARKINSON?
 72698 AIDS
 4605 HIV

L12 55 L11 AND (ALZHEIMER? OR PARKINSON? OR AIDS OR HIV)

=> d 40-55

40. 5,447,959, Sep. 5, 1995, Method of using derivatives of long chain fatty alcohols to treat **neuronal** degradation; Jacques Borg, 514/725, 690, 693, 703, 715, 763 :IMAGE AVAILABLE:

41. 5,442,043, Aug. 15, 1995, Peptide conjugate; Makoto Fukuta, et al., 530/303, 304, 345, 394, 399, 409 :IMAGE AVAILABLE:

42. 5,428,012, Jun. 27, 1995, Oncostatin M and novel compositions having anti-neoplastic activity; Mohammed Shoyab, et al., 514/12; 424/85.1, 85.5; 514/21; 530/350 :IMAGE AVAILABLE:

43. 5,428,006, Jun. 27, 1995, Method of administering a biologically active substance; Erik Bechgaard, et al., 514/3, 2, 4; 530/303, 307, 311, 313 :IMAGE AVAILABLE:

44. 5,416,016, May 16, 1995, Method for enhancing transmembrane transport of exogenous molecules; Philip S. Low, et al., 435/375; 424/450; 435/172.3, 243; 514/2, 44 :IMAGE AVAILABLE:

45. 5,397,771, Mar. 14, 1995, Pharmaceutical preparation; Erik Bechgaard, et al., 514/2, 3, 4; 530/303, 307, 311, 313 :IMAGE AVAILABLE:

46. 5,243,094, Sep. 7, 1993, Derivatives of long chain fatty alcohols, their uses, particularly as cytotropic and cytoprotective molecules, and pharmaceutical compositions containing them; Jacques Borg, 568/822, 667, 668, 824 :IMAGE AVAILABLE:

47. 5,215,969, Jun. 1, 1993, Dopaminergic **neurotrophic** factor for

treatment of **Parkinson**'s disease; Joe E. Springer, et al., 514/21, 2 :IMAGE AVAILABLE:

48. 5,202,119, Apr. 13, 1993, Method of stimulating immune response; Ross G. Clark, et al., 424/204.1, 234.1, 277.1, 278.1; 514/2, 3 :IMAGE AVAILABLE:

49. 5,115,096, May 19, 1992, Amphiregulin: a bifunctional growth modulating glycoprotein; Mohammed Shoyab, et al., 530/322, 324 :IMAGE AVAILABLE:

50. 5,108,921, Apr. 28, 1992, Method for enhanced transmembrane transport of exogenous molecules; Philip S. Low, et al., 435/375, 243; 514/2, 44; 935/52 :IMAGE AVAILABLE:

51. 5,093,317, Mar. 3, 1992, Treating disorders by application of **insulin**-like **growth** factor; Michael E. Lewis, et al., 514/12; 424/556, 570; 514/3, 4, 21, 885, 903 :IMAGE AVAILABLE:

52. 5,057,494, Oct. 15, 1991, Method for preventing tissue damage after an ischemic episode; Warren D. Sheffield, 514/12, 21 :IMAGE AVAILABLE:

53. 4,902,505, Feb. 20, 1990, Chimeric peptides for **neuropeptide** delivery through the blood-**brain** barrier; William M. Pardridge, et al., 424/85.7; 514/2, 3, 4; 530/302, 303, 311, 350, 351 :IMAGE AVAILABLE:

54. 4,863,902, Sep. 5, 1989, Treatment of cancer; Harunobu Amagase, et al., 514/12, 2, 21 :IMAGE AVAILABLE:

55. 4,801,575, Jan. 31, 1989, Chimeric peptides for **neuropeptide** delivery through the blood-**brain** barrier; William M. Pardridge, 514/4; 424/85.7; 514/2, 3; 530/302, 303, 311, 351; 930/21, 24, 80, 150, 160, 260, DIG.565, DIG.570, DIG.620, DIG.700, DIG.720 :IMAGE AVAILABLE:

=> d 55 kwic

US PAT NO: 4,801,575 :IMAGE AVAILABLE: L12: 55 of 55

TITLE: Chimeric peptides for **neuropeptide** delivery through the blood-**brain** barrier

ABSTRACT:
 Chimeric peptides adapted for delivering **neuropharmaceutical** agents, such as **neuropeptides** into the **brain** by receptor-mediated transcytosis through the blood-**brain** barrier. The chimeric peptides include a peptide which by itself is capable of crossing the blood-**brain** barrier by transcytosis at a relatively high rate. The transportable peptide is conjugated to a hydrophilic **neuropeptide** which by itself is transportable only at a very low rate into the **brain** across the blood-**brain** barrier. The resulting chimeric peptide is transported into the **brain** at a much higher rate than the **neuropeptide** alone to thereby provide an effective means for

introducing hydrophilic **neuropeptides** into the **brain** through the blood-**brain** barrier.

SUMMARY:

BSUM(2)

The present invention relates generally to the introduction of **neuropharmaceutical** agents into the **brain** by transcytosis across the blood-**brain** barrier. More particularly, the present invention relates to chimeric peptides which are capable of transporting **neuropharmaceutical** agents into the **brain** by receptor-mediated transcytosis across the blood-**brain** barrier.

SUMMARY:

BSUM(3)

The vertebrate **brain** has a unique capillary system which is unlike that in any other organ in the body. The unique capillary system has morphologic characteristics which make up the blood-**brain** barrier (BBB). The blood-**brain** barrier acts as a systemwide cellular membrane which separates the **brain** interstitial space from the blood.

SUMMARY:

BSUM(4)

The unique morphologic characteristics of the **brain** capillaries which make up the BBB are: (a) epithelial-like high resistance tight junctions which literally cement all endothelia of **brain** capillaries together, and (b) scanty pinocytosis or transendothelial channels, which are abundant in endothelia of peripheral organs. Due to the unique characteristics of the blood-**brain** barrier, hydrophilic drugs and peptides that readily gain access to other tissues in the body are barred from entry into the **brain** or their rates of entry are very low.

SUMMARY:

BSUM(5)

Various strategies have been developed for introducing those drugs into the **brain** which otherwise would not cross the blood-**brain** barrier. The most widely used strategies involve invasive procedures where the drug is delivered directly into the **brain**. The most common procedure is the implantation of a catheter into the ventricular system to bypass the blood-**brain** barrier and deliver the drug directly to the **brain**. These procedures have been used in the treatment of **brain** diseases which have a predilection for the meninges, e.g., leukemic involvement of the **brain**.

SUMMARY:

BSUM(6)

Although invasive procedures for the direct delivery of drugs to the **brain** ventricles have experienced some success, they have not been entirely successful because they only distribute the drug to superficial

areas of the **brain** tissues, and not to the structures deep within the **brain**. Further, the invasive procedures are potentially harmful to the patient.

SUMMARY:

BSUM(7)

Other approaches to circumventing the blood-**brain** barrier utilize pharmacologic-based procedures involving drug latentiation or the conversion of hydrophilic drugs into lipid-soluble drugs. The majority of the . . . carboxyl and primary amine groups on the drug to make it more lipid-soluble and therefore more easily transported across the blood-**brain** barrier. Although the pharmacologic approaches have been used with some success, they may not be entirely satisfactory for delivery of. . .

SUMMARY:

BSUM(8)

Another approach to circumventing the blood-**brain** barrier involves the intra-arterial infusion of hypertonic substances which transiently open the blood-**brain** barrier to allow passage of hydrophilic drugs. However, hypertonic substances are potentially toxic and may damage the blood-**brain** barrier.

SUMMARY:

BSUM(9)

There presently is a need to provide improved substances and methods for delivering hydrophilic drugs and peptides across the blood-**brain** barrier and into the **brain**. It is desirable that such improved substances and methods provide for uniform introduction of the hydrophilic peptide or drug throughout the **brain** and present as little risk to the patient as possible.

SUMMARY:

BSUM(11)

In accordance with the present invention, new procedures and substances are disclosed which provide uniform distribution of **neuropeptides** and other drugs throughout the **brain** while reducing the problems inherent in prior invasive and pharmacologic drug introduction procedures.

SUMMARY:

BSUM(12)

The present invention is based on the surprising discovery that hydrophilic peptides may be physiologically transported across the blood-**brain** barrier by coupling or conjugating the drug to a transportable peptide which is capable of crossing the blood-**brain** barrier by receptor-mediated transcytosis. This discovery is particularly surprising in view of the traditional notion that the blood-**brain**

barrier is a passive barrier which is impenetrable by hydrophilic drugs or peptides.

SUMMARY:

BSUM(13)

The invention involves novel chimeric peptides which are adapted to deliver a **neuropharmaceutical** agent into the **brain** by transcytosis across the blood-**brain** barrier. The chimeric peptides include a transportable peptide that is capable of crossing the blood-**brain** barrier at relatively high rate by receptor-mediated transcytosis. The transportable peptide is conjugated with a **neuropharmaceutical** agent to form the chimeric peptide. The **neuropharmaceutical** agent is generally a hydrophilic peptide that does not by itself significantly cross the BBB. The conjugation of transportable peptides with **neuropharmaceutical** agents was surprisingly found to produce chimeric peptides which were capable of being transported across the blood-**brain** barrier.

SUMMARY:

BSUM(14)

As a feature of the present invention, the chimeric peptides are believed to be transported across the blood-**brain** barrier by the physiologic process of transcytosis via receptors in the blood-**brain** barrier. This insures that the chimeric peptide is distributed uniformly to all parts of the **brain**. In addition, the introduction of the chimeric peptide into the **brain** by a physiologic pathway reduces the harmful side effects and risks inherent in the traditional invasive and pharmacological approaches.

DETDESC:

DETD(2)

The chimeric peptides in accordance with the present invention are useful in delivering a wide variety of **neuropharmaceutical** agents to the **brain**. The invention is particularly well suited for delivering **neuropharmaceutical** agents which are hydrophilic peptides. These hydrophilic peptides are generally not transported across the blood-**brain** barrier to any significant degree.

DETDESC:

DETD(3)

Exemplary hydrophilic peptide **neuropharmaceutical** agents are: thyrotropin releasing hormone (TRH)—used to treat **spinal** cord injury and Lou Gehrig's disease; vasopressin—used to treat amnesia; alpha interferon—used to treat multiple sclerosis; somatostatin—used to treat **Alzheimer's** disease; endorphin—used to treat pain; L-methionyl (sulfone)-L-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-L-phenylalanine (an analogue of adrenocorticotrophic hormone (ACTH)-4-9)—used to treat epilepsy; and muramyl dipeptide—used to treat insomnia. All of these **neuropharmaceutical** peptides are available commercially or they may be isolated from natural sources by well-known techniques.

DETDESC:

DETD(4)

The following description will be limited to chimeric peptides in which the **neuropharmaceutical** agents are hydrophilic peptides (**neuropeptides**) with it being understood that the invention has application to any **neuropharmaceutical** agent which by itself is transported at a low or non-existent rate across the blood-**brain** barrier. The invention also has application where it is desired to increase the rate at which the **neuropharmaceutical** agent is transported across the blood-**brain** barrier.

DETDESC:

DETD(5)

The chimeric peptide includes the hydrophilic peptide drug conjugated to a transportable peptide which is capable of crossing the blood-**brain** barrier by transcytosis at a much higher rate than the hydrophilic **neuropeptides**. Suitable transportable peptides include: **insulin**, transferrin, **insulin**-like **growth** **factor** I (**IGF**-I), **insulin**-like **growth** **factor** II (**IGF**-II), basic albumin and prolactin.

DETDESC:

DETD(7)

Insulin, **IGF**-I and **IGF**-II are also commonly available. Insulin is available on a wide scale commercially and may also be recovered from natural sources by well-known techniques. **IGF**-I and **IGF**-II are available from commercial outlets such as Amgen or Peninsula Labs or they may be isolated from natural sources according.

DETDESC:

DETD(8)

Basic . . . (pI) of 8.5 as compared to a pI of 3.9 for natural albumin. Cationized albumin, unlike natural albumin, enters the **brain** rapidly across the blood-**brain** barrier. Cationized albumin (pI=8.5) is prepared preferably by covalent coupling of hexamethylene-diamine (HMD) to bovine serum albumin (pI=3.5) according to.

DETDESC:

DETD(10)

The chimeric peptides are made by conjugating a transportable peptide with the **neuropharmaceutical** peptide.

DETDESC:

DETD(11)

The . . . transportable peptide) together without denaturing them. Preferably, the linkage can be easily broken once the chimeric peptide

has entered the **brain**. Suitable examples of conjugation reagents include: glutaraldehyde and cystamine and EDAC. Conjugation of peptides using glutaraldehyde is described in Poznansky. . .

DETD(12)

DETD(12)

Examples . . . is somatostatin, thyrotropin releasing hormone (TRH), vasopressin, alpha interferon, endorphin, muramyl dipeptide or ACTH 4-9 analogue; and B is insulin, **IGF-I**, **IGF-II**, transferrin, cationized (basic) albumin or prolactin.

DETD(18)

DETD(18)

The . . . procedure including parenteral injection or intranasal inhalation. Preferably, the chimeric peptides are combined with a compatible pharmaceutical carrier and injected **parenterally** or if desired combined with a suitable carrier and **administered** intranasally in accordance with the well-known conventional procedures used for intranasal administration of insulin. Suitable carrier solutions include those commonly. . . The concentration of a chimeric peptide in the carrier will vary depending upon the specific transportable peptide and the specific **neuropharmaceutical** peptide. Preferably, levels of the chimeric peptide in the carrier should be between about 0.001 weight percent to 0.01 weight. . . chimeric peptides present in the injection or intranasal solution should correspond to the accepted and established dosages for the particular **neuropharmaceutical** peptide as well as the transportable peptide.

DETD(22)

DETD(22)

Somatostatin, a peptide deficient in the **brain** of **Alzheimer's** disease, is a peptide which is not transported through the blood-**brain** barrier. Conversely, insulin is a peptide that is transported through the blood-**brain** barrier. The transportability of insulin through the blood-**brain** barrier is set forth in my article entitled "Receptor-Mediated Peptide Transport Through The Blood-**Brain** Barrier" (Endocrine Reviews, Vol. 7, No. 3, August 1986), the contents of which is hereby incorporated by reference.

DETD(29)

DETD(29)

Brain Microvessels and .sup.3 H-Somatostatin-.sup.125 I-Insulin Chimera

DETD(30)

DETD(30)

Somatostatin . . . using chloramine T and .sup.125 I-iodine. The two compounds were coupled together using SPDP as described in Example 1. Bovine **brain** microvessels were isolated as described in Pardridge, et al., "Rapid Sequestration And Degradation Of Somatostatin Analogues By Isolated **Brain** Microvessels", (Journal of **Neurochemistry**, Vol. 44, No. 4, 1985, pp. 1178-1184).

DETD(31)

DETD(31)

.sup.3 . . . somatostatin. The uptake of the free somatostatin likely represents nonspecific binding as described in the article mentioned above (Journal of **Neurochemistry**, Vol. 44, No. 4, 1985).

DETD(32)

DETD(32)

This . . . of somatostatin-insulin chimera via the insulin receptor. Previous studies have shown that the receptor-mediated endocytosis of peptides in the isolated **brain** microvessels is a reliable index of the in vivo blood-**brain** barrier receptor transport activity of peptides in vivo (see my previously-mentioned article in Endocrine Reviews, Vol. 7, No. 3, August. . .

DETD(34)

DETD(34)

A . . . resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight percent chimeric peptide which is **administered** to the patient **parenterally** or intranasally.

DETD(36)

DETD(36)

A . . . resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight percent chimeric peptide which is **administered** to the patient **parenterally**.

DETD(38)

DETD(38)

A . . . resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight percent chimeric peptide which is **administered** to the patient or subject **parenterally** or intranasally.

DETD(40)

DETD(40)

A chimeric peptide is prepared according to the same procedure as in Example 1 except that **IGF-II** is coupled to beta-endorphin. The resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight percent chimeric peptide which is **administered** to the patient or subject **parenterally** or intranasally.

DETD(42)

A . . . resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight percent chimeric peptide which is **administered** to the patient or subject **parenterally** or intranasally.

DETD(44)

A . . . resulting chimeric peptide is combined with sterile saline to provide a solution containing 0.01 weight percent chimeric peptide which is **administered** to the patient or subject **parenterally** or intranasally.

CLAIMS:

CLMS(1)

What is claimed is:

1. A chimeric peptide adapted for delivering a **neuropharmaceutical** agent into the **brain** by transcytosis through the blood-**brain** barrier, said chimeric peptide comprising: a transportable peptide capable of crossing the blood-**brain** barrier by transcytosis, said peptide being selected from the group consisting of insulin, transferrin, **IGF**-I, **IGF**-II, basic albumin and prolactin; and a **neuropharmaceutical** agent selected from the group consisting of somatostatin, thyrotropin releasing hormone, vasopressin, alpha interferon, endorphin, muramyl dipeptide and L-methionyl(sulfone)-L-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-L-phenylalanine, wherein said **neuropharmaceutical** agent is conjugated with said transportable peptide.

CLAIMS:

CLMS(2)

2. A chimeric peptide according to claim 1 wherein said transportable peptide and **neuropharmaceutical** agent are conjugated via a conjugation agent.

CLAIMS:

CLMS(3)

3. A chimeric peptide according to claim 2 wherein said conjugation agent is capable of conjugating the transportable peptide to said **neuropharmaceutical** agent by peptide thiolation or lysine coupling via glutaraldehyde.

CLAIMS:

CLMS(5)

5. A chimeric peptide according to claim 4 wherein said **neuropharmaceutical** agent is somatostatin.

CLAIMS:

CLMS(6)

6. A chimeric peptide according to claim 1 having the formula **STR3** wherein A is said **neuropharmaceutical** agent and B is said transportable peptide.

CLAIMS:

CLMS(10)

10. A method for delivering a **neuropharmaceutical** agent into the **brain** of an animal by transcytosis through the blood-**brain** barrier comprising the step of introducing a chimeric peptide into the bloodstream of said animal in a sufficient amount to provide transport of said chimeric peptide across said blood-**brain** barrier, wherein said chimeric peptide comprises a transportable peptide capable of crossing the blood-**brain** barrier conjugated with a **neuropharmaceutical** agent.

CLAIMS:

CLMS(12)

12. In a method for introducing a **neuropharmaceutical** agent into the **brain** across the blood-**brain** barrier, wherein the improvement comprises increasing the rate at which said **neuropharmaceutical** agent crosses the blood-**brain** barrier by conjugating said **neuropharmaceutical** agent with a transportable peptide capable of crossing the blood-**brain** carrier by transcytosis.

CLAIMS:

CLMS(13)

13. A method according to claim 10 wherein said transportable peptide is selected from the group consisting of insulin, transferrin, **IGF**-I, **IGF**-II, basic albumin and prolactin.

CLAIMS:

CLMS(14)

14. A method according to claim 10 wherein said **neuropharmaceutical** agent is a hydrophilic peptide.

CLAIMS:

CLMS(15)

15. A method according to claim 14 wherein said **neuropharmaceutical** agent is selected from the group consisting of somatostatin, thyrotropin releasing hormone, vasopressin, alpha interferon, endorphin, muramyl

dipeptide and L-methionyl(sulfone)-L-glutamyl-L-histidyl-L-phenylalanyl-D-lysyl-L-phenylalanine.

CLAIMS:

CLMS(16)

16. A method according to claim 10 wherein said transportable peptide and **neuropharmaceutical** agent are conjugated via a conjugation agent.

CLAIMS:

CLMS(17)

17. A method according to claim 16 wherein said conjugation agent is capable of conjugating the transportable peptide to said **neuropharmaceutical** agent by peptide thiolation or lysine coupling via glutaraldehyde.

CLAIMS:

CLMS(19)

19. A method according to claim 18 wherein said **neuropharmaceutical** agent is somatostatin.

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US PAT NO: 5,215,969 :IMAGE AVAILABLE: L12: 47 of 55

TITLE: Dopaminergic **neurotrophic** factor for treatment of **Parkinson's** disease

ABSTRACT:

Dopaminergic **Neurotrophic** Factor (DNTF), derived from cells of the peripheral **nervous** system, is administered to patients suffering from **Parkinson's** Disease in an amount effective to facilitate survival of substantia nigra dopamine **nerve** cells.

SUMMARY:

BSUM(1)

The present invention relates to a composition of matter, derived from cells of the peripheral **nervous** system, comprising dopaminergic **neurotrophic** factor, to a pharmaceutical preparation containing the dopaminergic neurotrophic factor, and to its use in the treatment of **Parkinson's** disease.

SUMMARY:

BSUM(2)

Parkinson's disease is a **neurodegenerative** disorder of the basal ganglia affecting specific populations of **neurons** in the **central** **nervous** system. Symptoms of **Parkinson's** disease include tremor at rest, muscular rigidity, akinesia and bradykinesia.

SUMMARY:

BSUM(3)

The primary **neuropathology** associated with this disorder is the progressive and persistent loss of dopaminergic **neurons** originating in the substantia nigra and projecting into the striatum. This, in turn, leads to a substantial decrease in the enzymes responsible for the synthesis of the **neurotransmitter**, dopamine. The subsequent decrease in dopamine synthesis correlates with the onset and severity of the above-noted symptoms.

SUMMARY:

BSUM(4)

Evidence indicating that the loss of dopaminergic **neurons** is causally connected with the symptoms associated with **Parkinson's** disease was found in 1983. Specifically, certain drug abusers who injected a toxin, known as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), as a heroin substitute developed signs of **parkinsonism** soon after injection. It was subsequently determined that MPTP is converted to a form (MPP+) that accumulates in substantia nigra dopamine **neurons** where it acts as a toxin destroying these **neurons**. The resultant loss of dopaminergic **neurons** was found to mimic the **neuropathology** observed in **Parkinson's** disease.

SUMMARY:

BSUM(5)

Studies have shown that **Parkinson's** disease, as well as other **neurodegenerative** disorders such as **Alzheimer's** disease and amyotrophic lateral sclerosis (ALS), may occur due to the loss or decreased availability of a **neurotrophic** substance specific for a particular population of **neurons** affected in each disorder. As used herein, "**neurotrophic** factor" refers to a substance or combination of substances whose primary function is to increase and/or maintain the survival of a **neuronal** population, but may also affect the outgrowth of **neuron** processes (**neurite**-promoting factors), and the metabolic activity of a **neuron**. The specific **neurotrophic** factor is synthesized, stored, and/or released from the target area of the degenerating **neurons**, bound and internalized by specific receptors, and transported in a retrograde fashion to the **neuron** body where it exerts its trophic effects well into adulthood. It may be the loss of such specific **neurotrophic** factors which is responsible for age-related declines in cell survival and/or function. While the cellular source remains unclear, there is evidence to suggest that **neurons** and glia are both capable of secreting **neurotrophic** factors.

SUMMARY:

BSUM(6)

Several putative **neurotrophic** factors effecting specific **neuronal** populations in the **central nervous** system have been reported. For example, it is postulated that **Alzheimer's** disease is the result of the loss or decreased availability of **nerve** growth factor (NGF), a polypeptide of approximately 13,000 dalton molecular weight in the monomer form. NGF is known to increase the survival, function and regeneration of cholinergic **neurons** in the basal forebrain. This population of cholinergic **neurons** has been shown to shrink and/or die in patients having **Alzheimer's** disease, and may be the primary **neuronal** defect responsible for the profound cognitive deficits associated with **Alzheimer's** disease. Recent studies have demonstrated that NGF is synthesized and released from the target areas of these cholinergic **neurons**, which are the hippocampal formation and the neocortex. Thoenen, H. et al., Rev. Physiol. Biochem. Pharmacol. 109:145-178 (1987); and Whittemore, S. R. et al., **Brain** Res. Rev. 12:439-464 (1987). Insofar as is known, there is no conclusive evidence that a loss of NGF production is the primary cause of degeneration of the basal forebrain cholinergic **neurons**. However, it has been proposed to treat **Alzheimer** patients by administering exogenous NGF, in order to increase the survival of degenerating **neuronal** populations.

SUMMARY:

BSUM(7)

At the present time, the therapy of choice for patients having **Parkinson's** disease is through stimulation of dopamine receptors in the striatum, which is the target area of substantia nigra **neurons**. This is achieved through "precursor drug therapy", involving the administration of .beta.-(3,4-dihydroxy phenyl)-.alpha.-alanine(L-DOPA/LEVODOPA), which passes the blood-**brain** barrier and is converted to dopamine. While this pharmacological approach is initially effective, L-DOPA treatment often becomes less effective over. . .

SUMMARY:

BSUM(8)

Numerous **neurotrophic** factors, in addition to NGF, which produce biological effects in the **central nervous** system have been reported, and these will be more specifically discussed hereinbelow. Insofar as is known, however, there is no currently available method for rescuing degenerating dopaminergic **neurons** in the substantia nigra. In addition, the conditions responsible for the onset of the degeneration of these **nerve** cells have not been elucidated. Thus, there is currently no clearly effective cure for **Parkinson's** disease.

SUMMARY:

BSUM(10)

In accordance with one aspect of the present invention, there is provided a purified and concentrated form of dopaminergic **neurotrophic** factor (DNTF) derivable from cultured cells of the mammalian peripheral **nervous** system. DNTF comprises a polypeptide having molecular weight of between about 9,000 and 10,000 daltons and exhibits a **neurotrophic** effect on substantia nigra dopamine **nerve** cells. Among the notable properties of DNTF is its ability to increase the survival time of fetal non-mitotic dopamine **nerve** cells in culture and to increase in vivo expression of tyrosine hydrosylase in substantia nigra dopamine **nerve** cells exposed to said factor.

SUMMARY:

BSUM(11)

In accordance with another aspect of this invention, there is provided a pharmaceutical preparation for the treatment of **Parkinson's** disease which comprises, as the active agent, the aforesaid DNTF in an amount sufficient to increase the survival and function of dopamine **nerve** cells located in the substantia nigra and projecting to the striatum, and, possibly, to cause regeneration of these cells.

SUMMARY:

BSUM(12)

In accordance with a further aspect of the present invention, there is provided a method for treating patients having **Parkinson's** disease, which comprises administering to such patients the above-described DNTF.

SUMMARY:

BSUM(13)

The present invention represents a potentially important alternative to current therapy used for treatment of **Parkinson's** disease. The precursor drug therapy (L-DOPA) now in use does not provide a cure for **Parkinson's** disease, but rather is a method of treatment that may become ineffective and even detrimental with prolonged use. It is anticipated that treatment of **Parkinson's** patients with the dopamine **neurotrophic** factor of the invention will inhibit or halt the progress of the disease by reducing the degeneration and dysfunction of substantia nigra **nerve** cells. In addition, dopamine **neurotrophic** factor treatment may be useful in transplantation strategies where dopamine cells are transplanted as a means of replacing lost dopamine function. Specifically, dopaminergic **neurotrophic** factor may be administered in conjunction with **central nervous** system grafts of dopamine-synthesizing tissue in order to enhance the survival and function of the grafted tissue.

SUMMARY:

BSUM(14)

The dopaminergic **neurotrophic** factor of the invention that is

responsible for the observed activity against **Parkinson's** disease appears to comprises a polypeptide of approximately 9,500 daltons in molecular weight. However, the possibility that the factor may. . .

SUMMARY:

BSUM(15)

Although numerous **neurotrophic** factors having biological effects in the **central nervous** system have previously been reported, including factors derived from cells of the peripheral **nervous** system, none of the factors obtained heretofore are believed to exhibit physical or biological properties identical to the dopaminergic **neurotrophic** factor of the invention, as will be shown hereinbelow. Moreover, attempts previously made to recover a DNTF from the striatum, . . . by evidence supporting its presence there, has not led to the successful isolation of such factor Tomozawa, Y. et al., **Brain** Research, 399:111-124 (1986).

SUMMARY:

BSUM(17)

As noted above, the primary symptoms of **Parkinson's** disease are caused by a defect in a specific **neurotransmitter** system, the nigrostriatal dopamine system. Specifically, dopamine **neurons** in the substantia nigra degenerate, resulting in the loss of dopamine input to the striatum and the onset of characteristic. . .

SUMMARY:

BSUM(18)

One possible explanation for the degeneration of the dopamine-containing **nerve** cells is that a specific dopamine **neurotrophic** factor becomes ineffective, unavailable or is no longer synthesized by the target regions in the striatum. In addition, most **neurotrophic** factors function through specific membrane-bound receptors located on presynaptic terminals. Alterations in the function of these receptors would tend to render the **neurotrophic** factor ineffective. In a normal, healthy individual, dopamine **neurotrophic** factor is released from the target region of these dopamine-containing substantia nigra **nerve** cells in the striatum. This factor is recognized and bound by specific receptors, then internalized as a complex and transported in a retrograde fashion to the cell body of the **nerve** cell where it functions to maintain dopamine **neuron** survival and normal homeostatic function. In the case of **Parkinson's** disease, by comparison, the striatum may no longer be providing an adequate supply of the dopaminergic **neurotrophic** factor, resulting in dopamine **nerve** cells that are no longer able to function adequately and may eventually die due to the loss of the dopaminergic **neurotrophic** factor.

SUMMARY:

BSUM(19)

The . . . this invention comprises a soluble polypeptide of molecular

weight approximately 9,500 daltons which is extractable from cells of the peripheral **nervous** system. While the peripheral **nerve** is not a target of the **central nervous** system dopamine **nerve** cells, the cells associated with the peripheral **nerve** are known to synthesize and secrete a number of different trophic factors, e.g. NGF, especially following denervation.

SUMMARY:

BSUM(20)

The extraction of DNTF is performed on peripheral **nerve** preparations that have been incubated in low-serum or serum-free culture medium. In a preferred embodiment, Schwann cells (which are derived from the sciatic **nerve**) are utilized. Protease inhibitors, such as leupeptin, may be included in the culture medium in order to minimize the degradation of proteins secreted by the peripheral **nerve** cells.

SUMMARY:

BSUM(21)

A . . . exclusion capabilities. For example, Centricon.RTM.-10 and -30 (Amicon) centrifuge filtration tubes may be used to obtain fractions from the peripheral **nerve** preparation. This procedure allows for the isolation of a first fraction comprising molecules of molecular weight less than 10 kilodaltons. . . (Centricon-10) and a second fraction comprising molecules of molecular weight less than 30 kilodaltons (Centricon-30). The greatest amount of dopamine **neurotrophic** activity is exhibited by the filtrate obtained from the Centricon-10 tubes. The second fraction (molecular weight range between 10,000-30,000 daltons) includes a molecule or molecules that cause(s) dramatic increases in the outgrowth of **neuron** processes in dopamine-containing **nerve** cells in culture.

SUMMARY:

BSUM(22)

Additional . . . an appropriate monoclonal antibody having binding affinity for the DNTF polypeptide. The desired product is then sterilized, lyophilized and its **neurotrophic** activity determined using the culture bioassay described below (see Example 2).

SUMMARY:

BSUM(23)

The . . . can be excised from an SDS gel (0.1% SDS), and the polypeptide eluted into culture media for treatment of dopaminergic **neurons**, and the polypeptide present in the 9,500 dalton band exhibits the biological activity of DNTF.

SUMMARY:

BSUM(26)

The dopamine **neurotrophic** activity of the recovered material is readily determined via bioassay. One method of assaying for **neurotrophic** activity is to determine biological activity in cultures of dopaminergic **nerve** cells. The DNTF polypeptide of the invention has been found to exhibit selective survival and survival-related effects, i.e. production of dopamine-synthesizing enzymes, on dopamine **nerve** cells using the culture bioassay. Other measures of dopaminergic **neurotrophic** activity, besides survival, include cell growth and metabolic functions associated with normal homeostatic function, such as high affinity dopamine uptake. Following incubation with fractions exhibiting dopaminergic **neurotrophic** activity, dissociated cell cultures are stained using tyrosine hydroxylase immunocytochemistry. Tyrosine hydroxylase is an enzyme necessary for the production of dopamine. Thus, by using antibodies to tyrosine hydroxylase, dopamine-containing **nerve** cells may be identified. Once the dopamine-containing **nerve** cells are identified, measures of cell size can be performed on culture treated with DNTF, as opposed to control treated. . .

SUMMARY:

BSUM(27)

Changes in the levels of tyrosine hydroxylase messenger RNA can also provide a measure of dopamine **neuronal** function. Recent advances in molecular biology, such as in situ hybridization, permit quantitative analysis of single genes in single **neurons**. Such techniques make it possible to study the effects of dopaminergic **neurotrophic** factor on tyrosine hydroxylase gene expression In vitro and in vivo and are currently being implemented toward that end.

SUMMARY:

BSUM(28)

Once . . . uptake mechanism. Using radioactive (.sup.3 H) dopamine, the high-affinity uptake of dopamine can be determined in cultures treated with dopaminergic **neurotrophic** factor or control solutions. Increases in dopamine uptake can indicate increased dopamine synthesis and release, a measure of metabolic function in such **nerve** cells.

SUMMARY:

BSUM(29)

Experiments have been performed, both in vitro and in vivo which demonstrate the **neurotrophic** effect of DNTF on substantia nigra dopamine **nerve** cells and its potential for effectively treating **Parkinson's** Disease. The nature of these experiments and their results are described hereinbelow.

SUMMARY:

BSUM(30)

Several . . . a classic model for screening dopamine-related compounds. Indeed, it has been shown in numerous laboratories that transplantation of fetal dopamine **neurons** can cause reversal of this behavioral deficit. Facilitation of this behavioral recovery over time can be accomplished using co-grafts of peripheral **nerve** capable of secreting DNTF and mesencephalic dopamine synthesizing cells. It appears that the peripheral **nerve** secretions (including DNTF) continue to affect the dopamine cells in the host following transplantation.

SUMMARY:

BSUM(31)

Other experiments conducted to date include the transplantation of peripheral **nerve** segments into aging test animals with the compromised dopamine system, i.e. decreased number of dopamine-containing **neurons** and decreased dopamine synthesis and content. The peripheral **nerve** graft greatly increases tyrosine hydroxylase staining in remaining substantia nigra **neurons**, as well as the number of tyrosine hydroxylase-containing **nerve** fibers.

SUMMARY:

BSUM(32)

These experimental results indicate that DNTF is most likely a soluble factor released in vitro and in vivo by peripheral **nerves**, which may be transported in a retrograde fashion to the cell bodies of substantia nigra **neurons**, so as to enhance their survival and function.

SUMMARY:

BSUM(33)

As noted above, numerous **neurotrophic** factors exhibit biological effects in the **central nervous** system, including factors derived from the peripheral **nervous** system. Some of the well-characterized factors are listed below in Table 1. DNTF is distinctly different from all of the **neurotrophic** factors listed in Table 1, notwithstanding that it shares certain characteristics with some of them.

SUMMARY:

BSUM(34)

TABLE 1

Purified and partially-purified neurotrophic factors, their effects in the central nervous system, and selected physical properties		
FACTOR	PROPER-EFFECTS	TIES
Nerve growth factor		
	survival of cholinergic	
	MW 13,000	
(NGF)*	neurons ,	pI 10.0
	neurite induction	

Ciliary ****neurotrophic****
 survival, MW 20,400
 factor (CNTF)*
****neurite**** outgrowth
 pI 5.0
****Brain****-derived survival, MW 12,300
****neurotrophic**** (additive with NGF)
 pI 10.1
 factor (BDNF)*
 Insulin-like growth
 survival, MW 7,100
 factor-II (****IGF****-II)
****neurite**** outgrowth
 Basic fibroblast
 survival, MW 16,400
 growth factor (bFGF)*
****neurite**** outgrowth
 pI 9.6
 Acidic fibroblast
****neurite**** outgrowth
 MW 15,800
 growth factor (aFGF) pI 5.0
 Striatal-derived
 survival of dopamine
 MW 14,000
****neuronotrophic****
 cells, ****neurite**** outgrowth
 factor
 Striatal extract
 survival of dopamine
 MW 1500-
 factors cells, ****neurite**** outgrowth,
 2200
 dopamine uptake

SUMMARY:

BSUM(35)

The asterisk indicates a factor derived from cells of the peripheral ****nervous**** system.

SUMMARY:

BSUM(36)

One of the characteristics of a true neurotrophic factor is the ability to increase the survival of ****central** **nervous** system (**CNS**)** ****neurons****. Based on this criterion, aFGF, listed in Table 1, is not a true neurotrophic factor, but rather may be regarded as a ****neurite****-promoting factor. Similarly, numerous other factors, including, for example, fibronectin, collagen and laminin, are able to promote ****neurite**** outgrowth, without appreciably influencing the survival of the ****neuronal**** population.

SUMMARY:

BSUM(37)

Among the ****neurotrophic**** factors, listed in Table 1, CNTF is synthesized by denervated peripheral ****nerves**** and influences the survival and outgrowth of numerous ****neuronal**** populations including ciliary ****neurons****, sympathetic ****neurons****, dorsal root ganglia and some centrally-derived ****neurons****. However, the DNTF of the present invention is lower in molecular weight than CNTF (approximately 9,500 for the DNTF polypeptide. . .

SUMMARY:

BSUM(38)

Another factor that may be secreted by peripheral ****nerves**** is bFGF. Although bFGF may be considered a true ****neurotrophic**** factor, at least two characteristics serve to distinguish bFGF from DNTF. First, the molecular weight of bFGF is greater than. . . weight of the DNTF polypeptide is about 9,500 daltons. Second, bFGF contains a heparin sulfate binding domain. Fractions of peripheral ****nerve**** conditioned medium that have been passed over a heparin sulfate column (removing bFGF from the fraction) continued to enhance ****neuron**** survival and ****neurite**** outgrowth in cultured dopamine ****neurons****. These data indicate that DNTF is not related to bFGF, since it appears to contain no heparin binding site and presumably exhibits its activity after bFGF has been removed from peripheral ****nerve**** cell culture fluids.

SUMMARY:

BSUM(39)

Gangliosides, a family of glycosphingolipids present in ****nerve**** tissues, may also be secreted by peripheral ****nerves****. While there is no evidence to indicate that gangliosides function as a survival or ****neurotrophic**** factor, it appears that the presence of gangliosides may potentiate ****neurotrophic**** activity. For example, gangliosides have been shown to potentiate the effects of NGF on cultured basal forebrain cholinergic ****neurons****. In addition, ganglioside treatment has been shown to enhance the regeneration (but not survival) of substantia nigra dopamine ****neurons**** following damage. Thus, the effects of gangliosides are not as specific as DNTF, and require the presence of other appropriate. . .

SUMMARY:

BSUM(40)

A recent report describes a peripheral ****nerve****-derived soluble factor(s) that increases the survival and ****neurite**** outgrowth of sensory ****neurons**** in culture. Windebank, A. J. et al., ****Brain**** Research, 385:197-200 (1986). While this report intimates that the factor described therein is novel, the molecular weight and biological properties. . .

SUMMARY:

BSUM(41)

Considering the striatum-recovered factors listed in Table 1, DNTF differs from striatal-derived ****neurotrophic**** factor in that its molecular weight is less than 14,000. Moreover, it has been suggested that striatal-derived ****neurotrophic**** factor may not be unique, but in fact exhibits properties not unlike those of BDNF and bFGF. Dal Toso, R. et al., J. ****Neurosci****, 8:733-745 (1988). Other factors are found in the striatum that fall within the molecular weight range of 1,500-2,200

daltons. These factors, however, are also found in high concentrations in non-dopaminergic **brain** regions, such as the hippocampus, amygdala and cerebral cortex, and also influence the high affinity uptake of gamma-amino-n-butyric acid (GABA). These data indicate that striatal extract factors may not necessarily be specific to dopamine **neurons**. The use of striatal factors as a diagnostic and therapeutic tool in the treatment of **Parkinson's** Disease is the subject of a separate patent application. See U.S. patent application Ser. No. 444,293, filed Nov. 24, 1982, . . .

SUMMARY:

BSUM(42)

Unlike DNTF, NGF does not exhibit a **neurotrophic** effect on substantia nigra dopamine **nerve** cells. The molecular weight of NGF is also higher than that of DNTF. DNTF is similarly distinguishable from BDNF on the basis of their relative molecular weights. **IGF-II** is produced in the **central nervous** system almost exclusively in the astroglia. The role of **IGF-II** in the peripheral **nervous** system appears to be related to synapse formation and denervated-induced fiber growth during development and regeneration. Specifically, **IGF-II** levels are highest in the target region (muscle fiber) during pre-and early post natal development. Transection of the sciatic **nerve** also results in increased **IGF-II** levels in mature denervated muscle fibers. **IGF-II** has been shown to increase the survival of NGF-sensory and sympathetic **neurons** in culture. However, direct evidence for **IGF-II** as a survival factor in the **central nervous** system is lacking.

SUMMARY:

BSUM(43)

Another **insulin**-related **growth factor**, **IGF-I** also is present in the **central nervous** system and is synthesized in **neuronal** and non-**neuronal** cells. **IGF-I**, which has a molecular weight of about 7,600 daltons, has been shown to undergo retrograde transport in the rat sciatic **nerve** and may play a role in peripheral **nerve** regeneration. In addition, **IGF-I** can act as a survival factor for cortical **neurons** in transferrin-supplemented medium. At the present time, no effects of **IGF-I** on survival or **neurite** outgrowth Of cultured dopamine **neurons** has been reported. Moreover, a recent study has shown that binding sites for **IGF-I** in the **central nervous** system are associated with cholinergic, and not dopaminergic **brain** regions. Araujo, D. M. et al., **Brain** Res., 484:130-138 (1989). Therefore, given the published results of this study

and our own test results, it appears that DNTF is not related to the **insulin** family of **growth factors**.

SUMMARY:

BSUM(44)

In sum, while there are numerous neurotrophic factors that have biological activities in the **central nervous** system, as set forth in Table 1 above, the apparent differences in properties between such factors and DNTF provides compelling. . .

SUMMARY:

BSUM(46)

It . . . association with the selected pharmaceutical carrier. The appropriate dosage unit to be administered for facilitating survival of substantia nigra dopamine **nerve** cells may be routinely determined by those skilled in the art. It is expected that the standard dosage unit will. . .

SUMMARY:

BSUM(47)

The pharmaceutical preparation is preferably **administered parenterally**, e.g. by introduction into the **central nervous** system of the patient. Such administration may be accomplished by intracerebroventricular infusion. Patients may also be treated with DNTF by transplanting into the striatum cells of the peripheral **nervous** system capable of releasing DNTF. Such cells may be cotransplanted with dopamine-synthesizing cells of the **central nervous** system, such as mesencephalic dopamine synthesizing cells. The treatments just described may also be administered in conjunction with one another. For example, dopamine synthesizing cells of the **central nervous** system may be transplanted into the striatum of a patient who is simultaneously being **administered** the pharmaceutical preparation of the invention. Non-**parenteral** routes may also be useful in **administering** DNTF, including oral, intranasal, rectal as well as ophthalmic administration. The pharmaceutical preparation of the invention may be administered at. . .

DETDESC:

DETD(5)

Rat sciatic **nerves** (approximately 2.5-3.0 cm in length) are placed in 1.0 ml. of sterile, serum-free culture medium containing protease inhibitors and incubated. . . fraction contained compounds of molecular weight of 30,000 daltons or less, which included substances that dramatically increased the outgrowth of **neurite** processes, i.e. **neurite** number, length and branching, in dopamine-containing **neurons** and culture. A third fraction comprised compounds of molecular weight in excess of 30,000 daltons which included substances which exhibited a **neurotoxin**-like effect on dopamine-containing **neurons**. Because DNTF is found in the fraction recovered in the

Centricon-10 centrifuge tube, isolation of DNTF can be initiated using this procedure. The DNTF-containing fraction was sterilized by passage through a 0.2 μ m filter, lyophilized and subjected to **neurotrophic** activity determination by culture bioassay.

DETD(7)

DETD(7)

The dopaminergic **neurotropic** factor of the present invention was purified from Schwann cells (which are derived from the sciatic **nerve** of the mammalian peripheral **nervous** system), according to the following procedure. Schwann cells were plated at an initial plating density of 200,000 cells/cc in low.

DETD(8)

DETD(8)

The . . . of purified DNTF polypeptide has been determined to be approximately 9,500 daltons, using SDS polyacrylamide gel electrophoresis. The purified dopaminergic **neurotrophic** factor has also been found to have the following characteristics: (1) it is a basic protein, as it does not. . . can be excised from an SDS gel (0.1% SDS), and the protein eluted into culture media for treatment of dopaminergic **neurons**, and the protein present in the 9,500 dalton band exhibits the biological activity of DNTF.

DETD(10)

DETD(10)

The . . . and EMBL protein databases, and was found to be unique. Thus, DNTF is indeed a novel molecule derivable from peripheral **nervous** system cells and having specific **neurotrophic** properties on ventral mesencephalon **neurons**.

DETD(13)

DETD(13)

Dissociation cultures of dopamine **nerve** cells were obtained using standard protocols. Specifically, 25 0.2-0.4 mm pieces of rat ventral mesencephalon (which included A8-A10 dopamine **nerve** cells) were dissected from embryonic day 13-16 rats. At this stage of development, the dopamine **nerve** cells were post mitotic, but did not yet innervate the striatum. Dissociated cell cultures were prepared by triturating the tissue.

DETD(16)

DETD(16)

Cultures of mesencephalic **nerve** cells were stained for tyrosine hydroxylase (TH) to identify dopaminergic **nerve** cells. Cultures were fixed with 5% acrolein, and prepared for immunocytochemistry utilizing

the Vectastain ABC technique (Vector Laboratories, Inc., Burlingame, Calif.). In this study, TH was utilized as a marker for developing midbrain DA **neurons**. TH antibody was obtained from Eugene Tech (Allendale, N.J.), and used in a dilution of 1:2,500.

DETD(17)

DETD(17)

Cultures . . . first fraction). This is probably due to the dilution of the DNTF in the higher molecular weight fraction. However, extensive **neurite** outgrowth was observed in cultures that were treated with the 10,000-20,000 m.w. from Example 1(a), as compared with all other treatments. While this **neurite**-promoting factor has not been conclusively identified, it exhibits properties similar to CNTF (see Table 1 above), which is found in relatively high concentrations in peripheral **nerve** extracts.

DETD(18)

DETD(18)

The . . . DNTF could not be blocked with antiserum to NGF or laminin and was partially induced by exposing the cultured dopamine **nerve** cells to the 10,000-20,000 molecular weight fraction from Example 1(a) for only 2 days, followed by 5 additional days in serum-free medium only. Thus, constant presence of DNTF may not be necessary to provide an effective level of **neuron** survival and function.

DETD(19)

DETD(19)

DNTF polypeptide purified by the method described in Example 1(b) exerted a similar effect on mesencephalic **nerve** cell number and survival.

DETD(23)

DETD(23)

The . . . weight fraction from Example 1(a) has been tested using three different conditions to determine its effects in vivo. Rat sciatic **nerve**, including the tibial and peroneal branches were stripped of the surrounding epineurium, cut into 5.0 mm segments, and washed repeatedly in sterile calcium-magnesium free medium containing 0.1% glucose, 100 μ g/ml streptomycin and 2.5 μ g/ml fungizone. These **nerve** segments were then loaded into the lumen of sterilized Amicon XM-50 fibers (1.1 mm ID; cut into 4.5 mm lengths),. . . serum, 2 mM L-glutamine, 0.45% glucose, 1 mM sodium pyruvate, 50 units per ml penicillin, and 50 μ g/ml streptomycin. The **nerve**-containing tubes were incubated in this solution for 1-2 days in a humid chamber of 95% air, 5% C..degree.2 at 37.degree.. . .

DETD(23)

DETD(24)

The hollow polymer fibers serve as carriers for subsequent transplantation of the **nerve** segments into the **central nervous** system. The polymer fibers comprise a semiporous membrane that allows for the exclusion of molecules of specified molecular weights. The . . .

DETD(25)

DETD(25)

The **nerve** tube implants thus prepared were transplanted into the lateral cerebral ventricle of young and aging normal rats for 2, 4, 8 or 10 weeks. In addition, the **nerve** tube implants were transplanted into young adult rats with unilateral lesions of the nigro-striatal dopamine system and co-grafts of fetal dopamine **nerve** cells (embryonic day 14). Lesions of the nigro-striatal dopamine system result in a well characterized unilateral rotation when the animals are challenged with dopamine agonists such as amphetamine. Transplants of fetal dopamine **neurons** have been found to reinnervate target areas denervated by the lesions, and to reverse the behavioral rotation.

DETD(26)

DETD(26)

In **brain** sections of animals that received only the **nerve** tube transplants, tyrosine hydroxylase staining was enhanced in the dopamine-containing **neurons** in the substantia nigra, as well as in **nerve** fibers located in the target region of these **neurons**. This effect was observed at 4, 8, and 10 weeks, but not at 2 weeks following transplantation. The presence of enhanced tyrosine hydroxylase staining in **neurons** distant to the **nerve** tube implant indicate that DNTF is a soluble factor that is transported specifically in dopamine-containing **nerve** cells.

DETD(27)

DETD(27)

Co-grafts of **nerve** tubes with fetal dopaminergic **neurons** into animals with unilateral lesions of the nigro-striatal dopamine system resulted in enhanced behavioral recovery as determined using the amphetamine-induced rotation. Immunohistochemical evaluation of the **brain** revealed enhanced tyrosine hydroxylase staining of grafted **neuron** cell bodies and axons. Invariably, fibers from the grafted **neurons** grew in the direction of the **nerve** tube implant, suggesting some "chemotactic" property. This phenomenon is not unexpected, for when a soluble source of a trophic factor is released from the **nerve** tube, the concentration of the trophic factor will be highest in proximity to the **nerve** tube, with concentration decreasing as the distance from the **nerve** tube increases. In this case, the

axons of the grafted **nerve** cells were attracted toward the gradient containing the highest concentration of trophic support.

DETD(30)

DETD(30)

Three (3) weeks following termination of the infusion period, the animals were sacrificed and **brain** sections were subjected to TH staining, as described in Example 3. **Brain** sections which had been subjected to DNTF infusion were compared with corresponding non-infused sections from the other side of the **brain**. An increase in TH staining intensity, as well as an increase in the number of fibers, was observed in the DNTF-infused **brain** sections, but not in the sections not subjected to DNTF infusion.

DETD(31)

DETD(31)

The . . . indicate that DNTF treatment in patients having Parkinson's Disease would provide a valuable alternative to present therapy by facilitating dopamine **neuron** survival in the substantia nigra, which present therapy is unable to achieve.

DETD(32)

DETD(32)

While . . . those skilled in the art. For example, while the DNTF of the invention is derivable from cells of the peripheral **nervous** system according to the isolation and purification procedures described above, it may also be derivable from such cells using recombinant. .

DETD(33)

DETD(33)

HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO
(v) FRAGMENT TYPE: N-terminal
(vi) ORIGINAL SOURCE:
(A) ORGANISM: Rat
(F) TISSUE TYPE: Sciatic **nerve**
(G) CELL TYPE: Schwann cells
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
XaaGluAspThrSerAsnIleAlaValAlaSerGlyXaaXaaPro
1510 15

CLAIMS:

CLMS(1)

What is claimed is:

1. A purified form of soluble dopaminergic **neurotrophic** factor derived from cultured cells of the mammalian peripheral **nervous** system, said factor comprising a polypeptide of molecular weight between about 9,000 and about 10,000 daltons, said factor being capable of increasing the survival time of fetal, non-mitotic dopamine **neurons** in culture, and of increasing in vivo expression of tyrosine hydroxylase in substantia nigra dopamine **nerve** cells exposed to said

factor, said factor having a ****neurotrophic**** effect on substantia nigra dopamine ****nerve**** cells.

CLAIMS:

CLMS(6)

6. A pharmaceutical preparation for the treatment of ****Parkinson****'s Disease which comprises, as an active ingredient, a purified form of soluble dopaminergic ****neurotrophic**** factor derived from cultured cells of the mammalian peripheral ****nervous**** system, said factor comprising a polypeptide of molecular weight between about 9,000 and about 10,000 daltons, said factor being capable of increasing the survival time of fetal, non-mitotic dopamine ****nerve**** cells in culture, and of increasing in vivo expression of tyrosine hydroxylase in substantia nigra dopamine ****nerve**** cells exposed to said factor, said factor having a ****neurotrophic**** effect on substantia nigra dopamine ****nerve**** cells, and a biologically acceptable medium.

CLAIMS:

CLMS(8)

8. A method for treating patients having ****Parkinson****'s Disease, which comprises administering to said patients the pharmaceutical preparation of claim 6.

CLAIMS:

CLMS(9)

9. A method as claimed in claim 8, wherein said pharmaceutical preparation is administered by introduction into the ****central**** ****nervous**** system of said patients.

CLAIMS:

CLMS(11)

11. A purified form of soluble dopaminergic ****neurotrophic**** factor derived from cultured cells of the mammalian peripheral ****nervous**** system, said factor comprising a polypeptide, the N-terminal portion of said polypeptide having the amino acid sequence ID No. 1: . . . represents an amino acid of mammalian proteins, said factor being capable of increasing the survival time of fetal, non-mitotic dopamine ****nerve**** cells in culture, and of increasing in vivo expression of tyrosine hydroxylase in substantia nigra dopamine ****nerve**** cells exposed to said factor, said factor having a ****neurotrophic**** effect on substantia nigra dopamine ****nerve**** cells.

=> d his

(FILE 'USPAT' ENTERED AT 16:21:01 ON 13 OCT 1997)

L1 2716 S (IGF## OR (INSULIN?(3A)(GROWTH FACTOR?)))

L2 706 S L1 AND (NERV? OR NEUR?)

L3 2854 S (IGF### OR (INSULIN?(3A)(GROWTH FACTOR?)))

L4 706 S L3 AND (NERV? OR NEUR?)

L5 361 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR NEUR?)) OR CNS)

L6 437 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR NEUR?)) OR CNS OR

SP

L7 381 S L4 AND (BRAIN OR (CENTRAL(3A)(NERV? OR NEUR?)) OR CNS OR

SP

L8 69 S L7 AND (PARENTERAL(5A)ADMINISTRAT?)

L9 1 S 4801575/PN

L10 1 S L9 AND ADMINISTER?

L11 108 S L7 AND (PARENTERAL?(10A)ADMINIST?)

L12 55 S L11 AND (ALZHEIMER? OR PARKINSON? OR AIDS OR HIV)

=> d 4-55 date

L12: 4 of 55

TITLE: Method to enhance permeability of the blood/****brain**** blood/****nerve**** barriers to therapeutic agents

US PAT NO: 5,670,477 DATE ISSUED: Sep. 23, 1997

:IMAGE AVAILABLE:

APPL-NO: 08/425,576 DATE FILED: Apr. 20, 1995

L12: 5 of 55

TITLE: Methods for the preparation of immunostimulating agents

for in vivo delivery

US PAT NO: 5,665,383 DATE ISSUED: Sep. 9, 1997

:IMAGE AVAILABLE:

APPL-NO: 08/488,804 DATE FILED: Jun. 7, 1995

REL-US-DATA: Continuation-in-part of Ser. No. 200,235, Feb. 22, 1994,

Pat. No. 5,498,421, which is a continuation-in-part of Ser. No. 23,698, Feb. 22, 1993, Pat. No. 5,439,686, and a continuation-in-part of Ser. No. 35,150, Mar. 26, 1993, Pat. No. 5,362,478.

L12: 6 of 55

TITLE: Methods for the preparation of pharmaceutically active agents for in vivo delivery

US PAT NO: 5,665,382 DATE ISSUED: Sep. 9, 1997

:IMAGE AVAILABLE:

APPL-NO: 08/485,448 DATE FILED: Jun. 7, 1995

REL-US-DATA: Continuation-in-part of Ser. No. 200,235, Feb. 22, 1994,

Pat. No. 5,498,421, which is a continuation-in-part of Ser. No. 23,698, Feb. 22, 1993, Pat. No. 5,439,686, and a continuation-in-part of Ser. No. 35,150, Mar. 26, 1993, Pat. No. 5,362,478.

L12: 7 of 55

TITLE: Methods and compositions for stimulating ****neurite**** growth

US PAT NO: 5,654,332 DATE ISSUED: Aug. 5, 1997

:IMAGE AVAILABLE:

APPL-NO: 08/486,004 DATE FILED: Jun. 8, 1995

L12: 8 of 55

TITLE: Secreted proteins and polynucleotides encoding them

US PAT NO: 5,654,173 DATE ISSUED: Aug. 5, 1997

:IMAGE AVAILABLE:

APPL-NO: 08/702,080 DATE FILED: Aug. 23, 1996

L12: 9 of 55

TITLE: OP-3-induced morphogenesis

US PAT NO: 5,652,337 DATE ISSUED: Jul. 29, 1997

:IMAGE AVAILABLE:

APPL-NO: 08/479,666 DATE FILED: Jun. 7, 1995
REL-US-DATA: Division of Ser. No. 971,091, Nov. 3, 1992,
abandoned,

which is a continuation-in-part of Ser. No. 922,813,
Jul. 31, 1992, abandoned, which is a
continuation-in-part of Ser. No. 752,764, Aug. 31, 1991,
abandoned, which is a continuation-in-part of Ser. No.
667,274, Mar. 11, 1991, abandoned, said Ser. No.
971,091, Nov. 3, 1992, abandoned is a
continuation-in-part of Ser. No. 923,780, Jul. 31, 1992,
abandoned, which is a continuation-in-part of Ser. No.
752,764, Aug. 30, 1991, abandoned, and a
continuation-in-part of Ser. No. 752,857, Aug. 30, 1991,
abandoned, each Ser. No. is a continuation-in-part of
Ser. No. 667,274, Mar. 11, 1991, abandoned, said Ser.
No. 971,091, Nov. 3, 1992, abandoned is a
continuation-in-part of Ser. No. 938,336, Aug. 28, 1992,
abandoned, and a continuation-in-part of Ser. No.
938,337, Aug. 28, 1992, abandoned, each Ser. No. is a
continuation-in-part of Ser. No. 753,059, Aug. 30, 1991,
abandoned, which is a continuation-in-part of Ser. No.
667,274, Mar. 11, 1991, abandoned, said Ser. No.
971,091, Nov. 3, 1992, abandoned is a
continuation-in-part of Ser. No. 938,021, Aug. 28, 1992,
abandoned, which is a continuation-in-part of Ser. No.
752,861, Aug. 30, 1991, abandoned, which is a
continuation-in-part of Ser. No. 667,274, Mar. 11, 1991,
abandoned, said Ser. No. 971,091, Nov. 3, 1992,
abandoned is a continuation-in-part of Ser. No. 945,285,
Sep. 15, 1992, abandoned, and a continuation-in-part of
Ser. No. 945,286, Sep. 15, 1992, abandoned, each Ser.
No. is a continuation-in-part of Ser. No. 752,764, Aug.
30, 1991, abandoned, said Ser. No. 971,091, Nov. 3,
1992, abandoned is a continuation-in-part of Ser. No.
946,235, Sep. 16, 1992, abandoned, and a
continuation-in-part of Ser. No. 946,238, Sep. 16, 1992,
abandoned, each Ser. No. is a continuation-in-part of
Ser. No. 752,764, Aug. 30, 1991, abandoned.

L12: 10 of 55

TITLE: Treating disorders by application of **insulin**-like
growth **factors** and analogs
US PAT NO: 5,652,214 DATE ISSUED: Jul. 29, 1997
:IMAGE AVAILABLE:
APPL-NO: 07/958,903 DATE FILED: Oct. 7, 1992
REL-US-DATA: Continuation-in-part of Ser. No. 869,913, Apr.
15, 1992,

abandoned, which is a continuation-in-part of Ser. No.
534,139, Jun. 5, 1990, abandoned, which is a
continuation-in-part of Ser. No. 361,595, Jun. 5, 1989,
Pat. No. 5,093,317.

L12: 11 of 55

TITLE: Nucleic acid encoding a novel morphogenic protein,
OP-3
US PAT NO: 5,652,118 DATE ISSUED: Jul. 29, 1997
:IMAGE AVAILABLE:
APPL-NO: 08/480,528 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation of Ser. No. 971,091, Nov. 3, 1992,
abandoned,

which is a continuation-in-part of Ser. No. 922,813,
Jul. 31, 1992, abandoned, which is a
continuation-in-part of Ser. No. 752,764, Aug. 31, 1991,
abandoned, which is a continuation-in-part of Ser. No.
667,274, Mar. 11, 1991, abandoned, said Ser. No.
971,091, Nov. 3, 1992, abandoned is a
continuation-in-part of Ser. No. 923,780, Jul. 31, 1992,
abandoned, which is a continuation-in-part of Ser. No.
752,764, Aug. 30, 1991, abandoned, and a
continuation-in-part of Ser. No. 752,857, Aug. 30, 1991,

abandoned, each Ser. No. is a continuation-in-part of
Ser. No. 667,274, Mar. 11, 1991, abandoned, said Ser.
No. 971,091, Nov. 3, 1992, abandoned is a
continuation-in-part of Ser. No. 938,336, Aug. 28, 1992,
abandoned, and a continuation-in-part of Ser. No.
938,337, Aug. 28, 1992, abandoned, each Ser. No. is a
continuation-in-part of Ser. No. 753,059, Aug. 30, 1991,
abandoned, which is a continuation-in-part of Ser. No.
667,274, Mar. 11, 1991, abandoned, said Ser. No.
971,091, Nov. 3, 1992, abandoned is a
continuation-in-part of Ser. No. 938,021, Aug. 28, 1992,
abandoned, which is a continuation-in-part of Ser. No.
752,861, Aug. 30, 1991, abandoned, which is a
continuation-in-part of Ser. No. 667,274, Mar. 11, 1991,
abandoned, said Ser. No. 971,091, Nov. 3, 1992,
abandoned is a continuation-in-part of Ser. No. 945,285,
Sep. 15, 1992, abandoned, and a continuation-in-part of
Ser. No. 945,286, Sep. 15, 1992, abandoned, each Ser.
No. is a continuation-in-part of Ser. No. 752,764, Aug.
30, 1991, abandoned, said Ser. No. 971,091, Nov. 3,
1992, abandoned is a continuation-in-part of Ser. No.
946,235, Sep. 16, 1992, abandoned, and a
continuation-in-part of Ser. No. 946,238, Sep. 16, 1992,
abandoned, each Ser. No. is a continuation-in-part of
Ser. No. 252,764, Aug. 30, 1991, abandoned.

L12: 12 of 55

TITLE: Methods for in vivo delivery of nutraceuticals and
compositions useful therefor
US PAT NO: 5,650,156 DATE ISSUED: Jul. 22, 1997
:IMAGE AVAILABLE:
APPL-NO: 08/482,272 DATE FILED: Jun. 7, 1995
REL-US-DATA: Continuation-in-part of Ser. No. 200,235, Feb.
22, 1994,

Pat. No. 5,498,421, which is a continuation-in-part of
Ser. No. 23,698, Feb. 22, 1993, Pat. No. 5,439,686, and
Ser. No. 35,150, Mar. 26, 1993, Pat. No. 5,362,478.

L12: 13 of 55

TITLE: Substituted amino alcohol compounds
US PAT NO: 5,641,783 DATE ISSUED: Jun. 24,
1997
:IMAGE AVAILABLE:
APPL-NO: 08/303,842 DATE FILED: Sep. 8, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 152,650, Nov.
12, 1993,
and Ser. No. 164,081, Dec. 8, 1993, Pat. No. 5,470,878.

L12: 14 of 55

TITLE: Methods for treating photoreceptors using glial cell
line-derived **neurotrophic** factor (GDNF) protein
product
US PAT NO: 5,641,750 DATE ISSUED: Jun. 24,
1997
:IMAGE AVAILABLE:
APPL-NO: 08/564,833 DATE FILED: Nov. 29, 1995

L12: 15 of 55

TITLE: Methods for the preparation of nucleic acids for in vivo
delivery
US PAT NO: 5,639,473 DATE ISSUED: Jun. 17,
1997
:IMAGE AVAILABLE: DISCL-DATE: Jun. 7, 2015
APPL-NO: 08/483,295 DATE FILED: Jun. 7, 1995
REL-US-DATA: Division of Ser. No. 200,235, Feb. 22, 1994, Pat.
No.

5,498,421, which is a continuation-in-part of Ser. No.
23,698, Feb. 22, 1993, Pat. No. 5,439,686, and a
continuation-in-part of Ser. No. 35,150, Mar. 26, 1993,
Pat. No. 5,362,478.

L12: 16 of 55

TITLE: Method for enhancing transmembrane transport of exogenous molecules
 US PAT NO: 5,635,382 DATE ISSUED: Jun. 3, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/349,407 DATE FILED: Dec. 5, 1994
 REL-US-DATA: Continuation of Ser. No. 851,544, Mar. 13, 1992, Pat. No.

5,416,016, which is a continuation of Ser. No. 498,762, Mar. 28, 1990, Pat. No. 5,108,921, Apr. 28, 1992, which is a continuation-in-part of Ser. No. 331,816, Apr. 3, 1989, abandoned.

L12: 17 of 55

TITLE: Methods for the preparation of blood substitutes for in vivo delivery
 US PAT NO: 5,635,207 DATE ISSUED: Jun. 3, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/480,621 DATE FILED: Jun. 7, 1995
 REL-US-DATA: Division of Ser. No. 200,235, Feb. 22, 1994, Pat. No.

5,498,421, which is a continuation-in-part of Ser. No. 23,698, Feb. 22, 1993, Pat. No. 5,439,686, and a continuation-in-part of Ser. No. 35,150, Mar. 26, 1993, Pat. No. 5,362,478.

L12: 18 of 55

TITLE: Linear somatostatin analogs
 US PAT NO: 5,633,263 DATE ISSUED: May 27, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/291,193 DATE FILED: Aug. 15, 1994
 REL-US-DATA: Continuation-in-part of Ser. No. 839,734, Feb. 19, 1992,

abandoned, which is a continuation-in-part of Ser. No. 343,325, Apr. 26, 1989, abandoned.

L12: 19 of 55

TITLE: **Brain**-enhanced delivery of **neuroactive** peptides by sequential metabolism
 US PAT NO: 5,624,894 DATE ISSUED: Apr. 29, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/428,488 DATE FILED: Apr. 27, 1995
 REL-US-DATA: Continuation of Ser. No. 946,062, Sep. 17, 1992, abandoned.

L12: 20 of 55

TITLE: Fused pyrrolo-2,3-c:carbazole-6-ones
 US PAT NO: 5,616,724 DATE ISSUED: Apr. 1, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/604,474 DATE FILED: Feb. 21, 1996

L12: 21 of 55

TITLE: Stimulation, production and culturing of hematopoietic progenitor cells by fibroblast growth factors
 US PAT NO: 5,612,211 DATE ISSUED: Mar. 18, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/076,875 DATE FILED: Jun. 15, 1993
 REL-US-DATA: Continuation-in-part of Ser. No. 950,549, Sep. 25, 1992,
 abandoned, which is a continuation-in-part of Ser. No. 536,108, Jun. 8, 1990, abandoned.

L12: 22 of 55

TITLE: Compositions and methods for enhanced drug delivery
 US PAT NO: 5,607,691 DATE ISSUED: Mar. 4, 1997
 :IMAGE AVAILABLE:

APPL-NO: 08/449,188 DATE FILED: May 24, 1995
 REL-US-DATA: Continuation of Ser. No. 164,293, Dec. 9, 1993, abandoned,

which is a continuation-in-part of Ser. No. 77,296, Jun. 14, 1993, abandoned, which is a continuation-in-part of Ser. No. 898,219, Jun. 12, 1992, abandoned, and a continuation-in-part of Ser. No. 9,463, Jan. 27, 1993, abandoned.

L12: 23 of 55

TITLE: Method to enhance permeability of the blood/**brain** blood/**nerve** barriers to therapeutic agents
 US PAT NO: 5,604,198 DATE ISSUED: Feb. 18, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/241,621 DATE FILED: May 12, 1994

L12: 24 of 55

TITLE: Enhanced loading of solutes into polymer gels
 US PAT NO: 5,603,955 DATE ISSUED: Feb. 18, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/276,462 DATE FILED: Jul. 18, 1994

L12: 25 of 55

TITLE: Method for treatment or prevention of obesity
 US PAT NO: 5,597,797 DATE ISSUED: Jan. 28, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/150,090 DATE FILED: Nov. 19, 1993
 PCT-NO: PCT/US93/10259 PCT-FILED: Oct. 26, 1993
 371-DATE: Nov. 19, 1993
 102(E)-DATE: Nov. 19, 1993
 PCT-PUB-NO: WO91/18621 PCT-PUB-DATE: Dec. 12, 1991

L12: 26 of 55

TITLE: Method induction of antigen-specific immune tolerance
 US PAT NO: 5,597,563 DATE ISSUED: Jan. 28, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/573,648 DATE FILED: Dec. 18, 1995
 REL-US-DATA: Continuation of Ser. No. 940,640, Sep. 4, 1992, abandoned.

L12: 27 of 55

TITLE: Fused pyrrolocarbazoles
 US PAT NO: 5,594,009 DATE ISSUED: Jan. 14, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/452,335 DATE FILED: May 26, 1995
 REL-US-DATA: Continuation-in-part of Ser. No. 427,160, Apr. 24, 1995,
 which is a continuation-in-part of Ser. No. 323,755, Oct. 14, 1994, Pat. No. 5,475,110.

L12: 28 of 55

TITLE: Ligand-mediated immunofunctional hormone binding protein assay method
 US PAT NO: 5,593,844 DATE ISSUED: Jan. 14, 1997
 :IMAGE AVAILABLE:
 APPL-NO: 08/441,357 DATE FILED: May 15, 1995
 REL-US-DATA: Continuation of Ser. No. 408,094, Mar. 21, 1995, which is
 a continuation of Ser. No. 39,093, Apr. 9, 1993, abandoned, which is a continuation-in-part of Ser. No. 615,538, Nov. 19, 1990, Pat. No. 5,210,017.

L12: 29 of 55

TITLE: Fused pyrrolocarbazoles
 US PAT NO: 5,591,855 DATE ISSUED: Jan. 7, 1997
 :IMAGE AVAILABLE:

APPL-NO: 08/427,160 DATE FILED: Apr. 24, 1995
REL-US-DATA: Continuation-in-part of Ser. No. 323,755, Oct.
14, 1994,
Pat. No. 5,475,110.

L12: 30 of 55

TITLE: Immunoconjugates comprising tyrosine kinase
inhibitors
US PAT NO: 5,587,459 DATE ISSUED: Dec. 24,
1996
:IMAGE AVAILABLE:
APPL-NO: 08/293,731 DATE FILED: Aug. 19, 1994

L12: 31 of 55

TITLE: Method of stimulating immune response
US PAT NO: 5,583,109 DATE ISSUED: Dec. 10,
1996
:IMAGE AVAILABLE:
APPL-NO: 08/404,621 DATE FILED: Mar. 13, 1995
REL-US-DATA: Continuation of Ser. No. 148,027, Nov. 4, 1993,
abandoned,
which is a continuation of Ser. No. 938,972, Sep. 1,
1992, abandoned, which is a continuation of Ser. No.
722,813, Jun. 28, 1991, Pat. No. 5,202,119.

L12: 32 of 55

TITLE: Method of administration of **IGF**-I
US PAT NO: 5,565,428 DATE ISSUED: Oct. 15,
1996
:IMAGE AVAILABLE:
APPL-NO: 08/447,292 DATE FILED: May 22, 1995

L12: 33 of 55

TITLE: Particles, method of preparing said particles and uses
thereof
US PAT NO: 5,531,925 DATE ISSUED: Jul. 2, 1996
:IMAGE AVAILABLE:
APPL-NO: 08/211,293 DATE FILED: Apr. 11, 1994
PCT-NO: PCT/SE92/00692 PCT-FILED: Oct. 2, 1992
371-DATE: Apr. 11, 1994
102(E)-DATE: Apr. 11, 1994
PCT-PUB-NO: WO93/06921 PCT-PUB-DATE: Apr.
15, 1993

L12: 34 of 55

TITLE: Octapeptide analogs of somatostatin having threonine at
the sixth position
US PAT NO: 5,506,339 DATE ISSUED: Apr. 9, 1996
:IMAGE AVAILABLE:
APPL-NO: 07/840,621 DATE FILED: Feb. 21, 1992
REL-US-DATA: Continuation-in-part of Ser. No. 447,876, Dec. 8,
1989,
abandoned.

L12: 35 of 55

TITLE: Composition useful for in vivo delivery of biologics and
methods employing same
US PAT NO: 5,498,421 DATE ISSUED: Mar. 12,
1996
:IMAGE AVAILABLE:
APPL-NO: 08/200,235 DATE FILED: Feb. 22, 1994
REL-US-DATA: Continuation-in-part of Ser. No. 23,698, Feb. 22,
1993,
Pat. No. 5,439,686, and a continuation-in-part of Ser.
No. 35,150, Mar. 26, 1993, Pat. No. 5,362,478.

L12: 36 of 55

TITLE: Transmucosal therapeutic composition
US PAT NO: 5,482,706 DATE ISSUED: Jan. 9, 1996
:IMAGE AVAILABLE:
APPL-NO: 08/049,402 DATE FILED: Apr. 16, 1993

FRN-PR. NO: 4-097947 FRN FILED: Apr. 17, 1992
FRN-PR. CO: Japan

L12: 37 of 55

TITLE: Use of relaxin in the treatment of bradycardia
US PAT NO: 5,478,807 DATE ISSUED: Dec. 26,
1995
:IMAGE AVAILABLE: DISCL-DATE: Nov. 24,
2009
APPL-NO: 07/902,637 DATE FILED: Jun. 23, 1992
REL-US-DATA: Continuation-in-part of Ser. No. 747,080, Aug.
19, 1991,
Pat. No. 5,166,191.

L12: 38 of 55

TITLE: Fused Pyrrolocarbazoles
US PAT NO: 5,475,110 DATE ISSUED: Dec. 12,
1995
:IMAGE AVAILABLE:
APPL-NO: 08/323,755 DATE FILED: Oct. 14, 1994

L12: 39 of 55

TITLE: Oncostatin M and novel compositions having anti-
neoplastic
activity
US PAT NO: 5,451,506 DATE ISSUED: Sep. 19,
1995
:IMAGE AVAILABLE:
APPL-NO: 08/078,707 DATE FILED: Jun. 16, 1993
REL-US-DATA: Continuation of Ser. No. 397,676, Oct. 2, 1989,
abandoned,
and a continuation-in-part of Ser. No. 46,846, May 4,
1987, Pat. No. 5,120,535, which is a
continuation-in-part of Ser. No. 935,283, Nov. 26, 1986,
abandoned, which is a continuation-in-part of Ser. No.
811,235, Dec. 20, 1985, abandoned, said Ser. No.
397,676
is a division of Ser. No. 144,574, Jan. 15, 1988,
abandoned, which is a continuation-in-part of Ser. No.
115,139, Oct. 30, 1987, abandoned.

L12: 40 of 55

TITLE: Method of using derivatives of long chain fatty alcohols
to treat **neuronal** degradation
US PAT NO: 5,447,959 DATE ISSUED: Sep. 5, 1995
:IMAGE AVAILABLE:
APPL-NO: 08/027,034 DATE FILED: Mar. 5, 1993
FRN-PR. NO: 89 13456 FRN FILED: Oct. 13, 1989
FRN-PR. CO: France
FRN-PR. NO: 90 01771 FRN FILED: Feb. 14, 1990
FRN-PR. CO: France
REL-US-DATA: Continuation of Ser. No. 720,816, Jul. 11, 1991,
Pat. No.
5,243,094.

L12: 41 of 55

TITLE: Peptide conjugate
US PAT NO: 5,442,043 DATE ISSUED: Aug. 15,
1995
:IMAGE AVAILABLE:
APPL-NO: 08/158,245 DATE FILED: Nov. 29, 1993
FRN-PR. NO: 4-318031 FRN FILED: Nov. 27, 1992
FRN-PR. CO: Japan

L12: 42 of 55

TITLE: Oncostatin M and novel compositions having anti-
neoplastic
activity
US PAT NO: 5,428,012 DATE ISSUED: Jun. 27,
1995
:IMAGE AVAILABLE: DISCL-DATE: Jun. 9, 2009

APPL-NO: 08/085,279 DATE FILED: Jul. 1, 1993
REL-US-DATA: Continuation of Ser. No. 428,195, Oct. 27, 1989,
abandoned, which is a division of Ser. No. 144,574, Jan.
15, 1988, abandoned, which is a continuation-in-part of
Ser. No. 115,139, Oct. 30, 1987, abandoned, and a
continuation-in-part of Ser. No. 46,846, May 4, 1987,
Pat. No. 5,120,535, which is a continuation-in-part of
Ser. No. 935,283, Nov. 26, 1986, abandoned, which is a
continuation-in-part of Ser. No. 811,235, Dec. 20, 1985,
abandoned.

L12: 43 of 55

TITLE: Method of administering a biologically active substance
US PAT NO: 5,428,006 DATE ISSUED: Jun. 27,
1995

:IMAGE AVAILABLE: DISCL-DATE: Mar. 14,

2012

APPL-NO: 08/151,802 DATE FILED: Nov. 15, 1993
REL-US-DATA: Continuation of Ser. No. 71,604, Jun. 4, 1993,
abandoned,
which is a continuation of Ser. No. 870,893, Apr. 20,
1992, abandoned, which is a division of Ser. No.
696,564, May 8, 1991, abandoned.

L12: 44 of 55

TITLE: Method for enhancing transmembrane transport of
exogenous
molecules

US PAT NO: 5,416,016 DATE ISSUED: May 16,
1995

:IMAGE AVAILABLE:

APPL-NO: 07/851,544 DATE FILED: Mar. 13, 1992
REL-US-DATA: Continuation of Ser. No. 498,762, Mar. 28, 1990,
Pat. No.

5,108,921, which is a continuation-in-part of Ser. No.
331,816, Apr. 3, 1989, abandoned.

L12: 45 of 55

TITLE: Pharmaceutical preparation
US PAT NO: 5,397,771 DATE ISSUED: Mar. 14,
1995

:IMAGE AVAILABLE:

APPL-NO: 08/118,683 DATE FILED: Sep. 10, 1993
FRN-PR. NO: 1170/90 FRN FILED: May 10, 1990

FRN-PR. CO: Denmark

FRN-PR. NO: 2075/90 FRN FILED: Aug. 30, 1990

FRN-PR. CO: Denmark

REL-US-DATA: Continuation of Ser. No. 791,651, Nov. 14, 1991,
abandoned, which is a continuation-in-part of Ser. No.
696,564, May 8, 1991, abandoned.

L12: 46 of 55

TITLE: Derivatives of long chain fatty alcohols, their uses,
particularly as cytotropic and cytoprotective
molecules, and pharmaceutical compositions containing
them

US PAT NO: 5,243,094 DATE ISSUED: Sep. 7, 1993

:IMAGE AVAILABLE:

APPL-NO: 07/720,816 DATE FILED: Jul. 11, 1991

FRN-PR. NO: 89 13456 FRN FILED: Oct. 13, 1989

FRN-PR. CO: France

FRN-PR. NO: 90 01771 FRN FILED: Feb. 14, 1990

FRN-PR. CO: France

PCT-NO: PCT/FR90/00742 PCT-FILED: Oct. 15,
1990

371-DATE: Jul. 11, 1991

102(E)-DATE: Jul. 11, 1991

PCT-PUB-NO: WO91/05754 PCT-PUB-DATE: May 2,
1991

L12: 47 of 55

TITLE: Dopaminergic **neurotrophic** factor for treatment of
Parkinson's disease

US PAT NO: 5,215,969 DATE ISSUED: Jun. 1, 1993

:IMAGE AVAILABLE:

APPL-NO: 07/804,340 DATE FILED: Dec. 9, 1991

REL-US-DATA: Continuation-in-part of Ser. No. 392,733, Aug.
11, 1989,
abandoned.

L12: 48 of 55

TITLE: Method of stimulating immune response

US PAT NO: 5,202,119 DATE ISSUED: Apr. 13,
1993

:IMAGE AVAILABLE:

APPL-NO: 07/722,813 DATE FILED: Jun. 28, 1991

L12: 49 of 55

TITLE: Amphiregulin: a bifunctional growth modulating
glycoprotein

US PAT NO: 5,115,096 DATE ISSUED: May 19,
1992

:IMAGE AVAILABLE:

APPL-NO: 07/297,816 DATE FILED: Jan. 17, 1989

REL-US-DATA: Continuation-in-part of Ser. No. 181,884, Apr.
15, 1988,

abandoned, which is a continuation-in-part of Ser. No.
148,327, Jan. 25, 1988, abandoned.

L12: 50 of 55

TITLE: Method for enhanced transmembrane transport of
exogenous
molecules

US PAT NO: 5,108,921 DATE ISSUED: Apr. 28,
1992

:IMAGE AVAILABLE:

APPL-NO: 07/498,762 DATE FILED: Mar. 28, 1990

REL-US-DATA: Continuation-in-part of Ser. No. 331,816, Apr. 3,
1989,
abandoned.

L12: 51 of 55

TITLE: Treating disorders by application of **insulin**-like
growth **factor**

US PAT NO: 5,093,317 DATE ISSUED: Mar. 3, 1992

:IMAGE AVAILABLE:

APPL-NO: 07/361,595 DATE FILED: Jun. 5, 1989

L12: 52 of 55

TITLE: Method for preventing tissue damage after an ischemic
episode

US PAT NO: 5,057,494 DATE ISSUED: Oct. 15,
1991

:IMAGE AVAILABLE:

APPL-NO: 07/227,579 DATE FILED: Aug. 3, 1988

L12: 53 of 55

TITLE: Chimeric peptides for **neuropeptide** delivery
through
the blood-**brain** barrier

US PAT NO: 4,902,505 DATE ISSUED: Feb. 20,
1990

:IMAGE AVAILABLE:

APPL-NO: 07/185,702 DATE FILED: Apr. 25, 1988

REL-US-DATA: Continuation-in-part of Ser. No. 891,867, Jul. 30,
1986,
Pat. No. 4,801,575.

L12: 54 of 55

TITLE: Treatment of cancer

US PAT NO: 4,863,902 DATE ISSUED: Sep. 5, 1989

:IMAGE AVAILABLE:

APPL-NO: 06/935,740 DATE FILED: Nov. 28, 1986
FRN-PR. NO: 60-268174 FRN FILED: Nov. 28, 1985
FRN-PR. CO: Japan
FRN-PR. NO: 60-268175 FRN FILED: Nov. 28, 1985
FRN-PR. CO: Japan
FRN-PR. NO: 61-116557 FRN FILED: May 21, 1986
FRN-PR. CO: Japan
FRN-PR. NO: 61-116558 FRN FILED: May 21, 1986
FRN-PR. CO: Japan

L12: 55 of 55

TITLE: Chimeric peptides for **neuropeptide** delivery
through

the blood-**brain** barrier

US PAT NO: 4,801,575 DATE ISSUED: Jan. 31, 1989

:IMAGE AVAILABLE:

APPL-NO: 06/891,867 DATE FILED: Jul. 30, 1986

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